

平成 30 年度

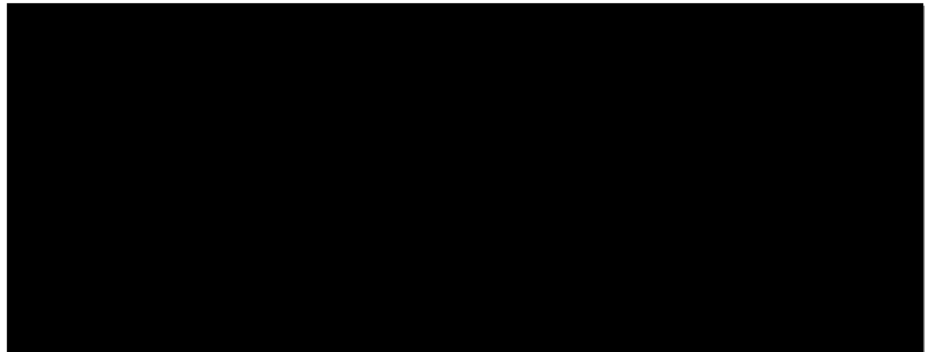
指定添加物の安全性に関する試験

p-サイメンのラットを用いる 90 日間反復経口投与毒性試験

機 関 名

研究責任者名

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1. 要約

指定添加物である *p*-サイメンをトウモロコシ油に混和して、0、12、60 および 300 mg/kg の用量で、雌雄とも各群 10 匹の Crl:CD (SD) ラットに 90 日間反復経口投与した。

- 1) 300 mg/kg 投与群の雌 1 例を投与第 45 日に切迫屠殺した。同例の一般状態の変化として、投与第 43 日から半眼、第 44 日から排便量が減少し、第 45 日の投与前に消瘦が認められた。同日の投与後には腹臥位、体温低下、自発運動の消失、死戦期呼吸、無便および無尿が認められたため、同日中に安楽死させた。その他の動物には投与期間中に死亡および切迫屠殺例はみられなかった。
- 2) 一般状態の変化として、投与後の一過性の流涎が 300 mg/kg 投与群の雌雄で散見された。排便量の減少が 300 mg/kg 投与群の雌 1 例で投与第 71~72 日に、赤色尿が同群の雌雄各 1 例で観察された。
- 3) 体重および摂餌量の変化として、体重減少が 300 mg/kg 投与群の雌で散見されたが、雌雄ともに対照群と比較して有意な差は認められなかった。摂餌量の減少が 300 mg/kg 投与群の雌で投与第 1 日に認められた。
- 4) 尿検査では、300 mg/kg 投与群の雄 1 例で尿潜血反応が認められ、尿沈渣中に赤血球が観察された。また、雌雄ともに尿量の増加、尿比重、尿中カリウムおよび塩素イオン濃度の減少が、雌では尿中ナトリウムイオン濃度の減少が認められたほか、雄では尿中ナトリウム、カリウムおよび塩素イオン総排泄量の増加が認められた。尿比重、ナトリウム、カリウムおよび塩素イオン濃度の減少は 60 mg/kg 投与群の雌でも認められた。
- 5) 血液学的検査では、300 mg/kg 投与群の雄で血色素量、ヘマトクリット値、MCH および MCHC の減少が、雌で血小板数および網状赤血球比率の減少が認められた。300 mg/kg 投与群の雌 1 例では、他の動物に比べて赤血球数、血色素量およびヘマトクリット値が低く、網状赤血球比率が高い傾向がみられた。血小板数の減少は 60 mg/kg 投与群の雌でも認められた。
- 6) 血液生化学的検査では、300 mg/kg 投与群の雌雄で尿素窒素濃度の増加および塩素イオン濃度の減少が、雄では、グルコース濃度の増加、AST および ALT 活性の上昇、トリグリセライド濃度の減少が、雌では γ -GTP 活性の上昇が認められた。グルコース濃度の増加は 60 mg/kg 投与群の雄、 γ -GTP 活性の上昇は同群の雌でも有意に認められた。
- 7) 器官重量測定では、300 mg/kg 投与群の雌雄で、肝臓の実重量および相対重量の増加、腎臓の相対重量の増加が認められた。また、同群の雄では腎臓の実重量の増加、精巣および精囊の実重量および相対重量の減少、雌では卵巣の実重量および相対重量の増加、下垂体の実重量の減少が認められた。肝臓重量の増加は 60 mg/kg 投与群の雄 (相対重量) および雌 (実重量および相対重量) でも認められた。脳の実重量の減少が 12、60 および 300 mg/kg 投与群の雄で認められた。
- 8) 切迫屠殺例の病理組織学的所見として、肝細胞がびまん性に肥大し、門脈周囲から小葉中間帯の肝細胞に細胞質空胞化がみられたほか、肝細胞の単細胞壊死が小葉中心性に認められた。腎臓の乳頭部では、うっ血および好中球浸潤を伴う乳頭壊死が先端部に、硝子滴が乳頭上皮および乳頭管にみられたほか、尿細管の再生が認められた。また、細胞質空胞化が尿細管上皮細胞に、びまん性の拡張が皮質の遠位尿細管および集合管に、鉍質沈着が髄質に認められた。その他、慢性進行性腎症が認められた。脾臓の白脾髄および赤脾髄は萎縮し、褐色色素沈着が認められた。胸腺、顎下リンパ節および腸間膜リンパ節は萎縮し、回腸のパイエル板ではリンパ球壊死が認められた。
- 9) 生存例の病理組織学的所見として、300 mg/kg 投与群では、小葉中心性の肝細胞肥大および肝細胞の単細胞壊死が雌雄で発生頻度および変化の程度ともに増加した。一方、門脈周囲性の肝細胞脂肪化は雄で発生頻度および変化の程度ともに減少し、クッパー細胞の褐色色素沈着が雌雄で認められた。腎臓では、腎乳頭壊死、腎乳頭先端部のうっ血、集合管の細胞質空胞化および皮質部遠位尿細管のびまん性の尿細管拡張が雌雄で発生頻度および変化の程度ともに増加した。また、腎乳頭上皮/乳頭管の硝子滴が雌雄で認められた。精巣では、精細管の変性/萎縮、ライディッヒ細胞のびまん性過形成および間質の水腫が、精巣上体では、管腔の精子減少および細胞残屑が発生頻度および変化の程度ともに増加した。精囊では萎縮がみられ

8) ロット番号

■■■■■

9) 保管条件

室温 (実測値 : 15~25°C)、遮光、暗所

10) 安定性

■■■■■において、投与開始前ならびに投与終了後に被験物質の性状 (目視による外観および色調) の確認および赤外吸収スペクトルを測定し、性状およびスペクトルに変化がないことを確認した。なお、測定は別試験 (試験番号 : ■■■■■) において GLP 下で確認した。

11) 入手先

日本香料工業会

12) 提供者

国立医薬品食品衛生研究所

13) 被験物質の保存

5g を ■■■■■ へ保存した。

5.2 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、Sprague-Dawley (SD) 系 [CrI:CD (SD)、SPF] ラット雌雄各 44 匹を 4 週齢で入手した。入荷日を含め 7 日間、検疫と馴化を兼ねて飼育した。検疫期間中、毎日一般状態を観察し、入荷日および検疫終了日に全例の体重を測定した。検疫期間中は、動物の尾に赤のフェルトペンで馴化番号を記入して個体識別を行った。飼育ケージには、試験番号、性、馴化番号および入荷日を記入した動物カードを掛けて識別した。入荷日および検疫終了日の体重は以下の通りであった。

動物入荷日 : ■■■■■

入荷時体重 : 雄 60.5~72.9 g (平均 67.1 g)、雌 66.9~76.8 g (平均 72.3 g)

検疫終了日 : ■■■■■

検疫終了時体重 : 雄 115.0~136.6 g (平均 125.8 g)、雌 110.9~136.9 g (平均 123.5 g)

検疫期間中、全ての動物の体重は順調に増加し、一般状態に異常は観察されなかった。群分けは、検疫終了時の体重を基に体重別に順位化し、体重別層化無作為抽出法で行った。群分けした動物には個体識別のため、耳パンチにより動物番号の下 2 桁の整数を標識した。飼育ケージには、群ごとに色識別した動物カードに試験番号、性、群および動物番号を記入して掛けた。投与開始時 (■■■■■) の体重は平均体重の±20%以内であった [雄:123.0~146.5 g (平均 134.2 g)、雌 : 120.2~139.1 g (平均 129.7 g)]。試験に使用しなかった余剰動物のうち、雌雄各 2 匹は微生物モニタリングに使用し、雄 2 匹は他試験に移管した。雌 2 例は剖検日 (■■■■■) に麻酔下で放血し、安楽死させた。

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、照明時間 12 時間 (7~19 時点灯) に設定された飼育室で、金属製金網床ケージ (220w×270d×190h mm、金属製休息板 130×150 mm 付) に 1 匹ずつ収容し、飼料 (固型 CE-2、ロット番号 : ■■■■■、日本クレア) および水道水 (■■■■■) を自由摂取させて飼育した。

飼育期間中の飼育室の温度の実測値は 23.0~24.0°C、湿度の実測値は 43.0~66.0%であり、いずれも許容範囲内であった。また、供給した飼料および水道水には試験に支障を来すような異常は認められなかった。供給した飼料は各ロット番号の分析試験成績書 (第 ■■■■■ 号、第 ■■■■■ 号、第 ■■■■■ 号、第 ■■■■■ 号) を、飲料水は水質検査結果書 (■■■■■) を確認し、当該報告書の写しを試験資料に保存した。

5.3 投与検体の調製

被験物質が水に不溶で、トウモロコシ油に溶解するため媒体はトウモロコシ油 (ロット番号 : ■■■■■、ナカライテスク) を選択した。

1) 調製方法

被験物質を秤量して、媒体を加えて混和し、75 mg/mL 溶液を調製した。さらに 75 mg/mL

溶液を媒体で希釈し、15 および 3 mg/mL 溶液を段階的に調製した。被験物質投与用量と濃度は以下の通り。調製した投与検体は室温 (実測値：23.0～24.0°C)、遮光下で保管し、調製後 8 日以内に使用した。

投与物質	投与用量 (mg/kg)	濃度 (mg/mL)
トウモロコシ油	0	0
p-サイメン	12	3
p-サイメン	60	15
p-サイメン	300	75

2) 安定性試験

300 ならびに 1 mg/mL の濃度の投与検体について、室温、遮光下における 8 日間の安定性を GLP 下で確認した (試験番号 [REDACTED])。

3) 含量試験

初回 ([REDACTED]) および投与期間中 ([REDACTED]) の投与検体の各濃度について、被験物質含量を測定した。その結果、初回測定では、各平均含量は調製濃度の 95.8% (3.00 mg/mL)、98.4% (15.0 mg/mL)、100.0% (75.0 mg/mL) であり、各測定値の相対標準偏差は 0.4% (3.00 mg/mL)、1.1% (15.0 mg/mL)、0.9% (75.0 mg/mL) であった。投与期間中の測定では、各平均含量は調製濃度の 96.8% (3.00 mg/mL)、99.0% (15.0 mg/mL)、100.5% (75.0 mg/mL) であり、各測定値の相対標準偏差は 0.6% (3.00 mg/mL)、0.2% (15.0 mg/mL)、0.1% (75.0 mg/mL) であった。初回および投与期間中のいずれも既定の範囲内であった。

4) 投与検体中の被験物質濃度測定法

Annex 2 に従った。

5.4 投与量の設定および投与方法

投与量は、「p-サイメンのラットを用いる 90 日間反復経口投与毒性試験のための予備試験」(試験番号 [REDACTED]) の結果を基に設定した。即ち、0 (媒体：トウモロコシ油)、100、300 および 1000 mg/kg/day の用量で被験物質を 5 週齢の雌雄ラットに 14 日間反復経口投与した。その結果、投与期間中、1000 mg/kg 投与群の雌 2 例が死亡した。1000 mg/kg 投与群の生存例では、流涎あるいは自発運動の低下のほか、体重増加抑制および摂餌量の減少が認められた。血液および血液生化学的検査では、1000 mg/kg 投与群の雄で血小板数および網状赤血球比率の減少、同群の雌で白血球数および好中球比率の増加が認められ、1000 mg/kg 投与群の雌雄でアルブミン濃度の増加し、同群の雌では、ALT、AST および γ -GTP 活性が増加し、電解質濃度が減少した。また、300 mg/kg 投与群の雌では尿素窒素濃度が増加し、1000 mg/kg 投与群の雌雄でも尿素窒素濃度が増加傾向を示した。病理学的検査では、300 および 1000 mg/kg 投与群の雌雄で、肝臓の実重量および相対重量が増加し、100 mg/kg 投与群の雌でも肝臓の相対重量が増加した。1000 mg/kg 投与群の雄では、腎臓および副腎の相対重量が増加し、脾臓の実重量が減少した。また、1000 mg/kg 投与群の精巣、精巣上体、前立腺および精囊、子宮の小型化も認められた。

以上の結果から、p-サイメンのラットを用いる 14 日間反復経口投与では 300 および 1000 mg/kg 投与群の雌雄で明らかな毒性変化が認められ、その程度は用量に関連した変化であった。投与期間が 90 日間であることを考慮し、本試験の投与量は、300 mg/kg を高用量とし、以下公比 5 で、60 mg/kg を中用量、12 mg/kg を低用量に設定した。

本被験物質は食品添加物として使用されていることから、毒性試験における投与方法は混餌投与による経口投与が望ましい。しかしながら、本被験物質は香料として使用されており、混餌投与では臭気が対照群へ影響することが想定された。そのため、げっ歯類の毒性試験における一般的な投与方法である強制経口投与を選択した。

投与は、雄は 90 日間、雌は 91 日間、1 日 1 回、9 時 00 分～11 時 19 分にフレキシブルタイプの胃管を用いて行った。投与回数および投与期間はガイドラインに拠った。

投与量、群構成および動物番号を以下に示した。

群	投与物質	投与用量 (mg/kg)	投与容量 ^{a)} (mL/kg)	濃度 (mg/mL)	動物番号	
					雄	雌
対照群	トウモロコシ油	0	4	0	M01001～ M01010	F01041～ F01050
低用量群	p-サイメン	12	4	3	M02011～ M02020	F02051～ F02060
中用量群	p-サイメン	60	4	15	M03021～ M03030	F03061～ F03070
高用量群	p-サイメン	300	4	75	M04031～ M04040	F04071～ F04080

a) 投与液量は最新測定時の体重をもとに個体別に算出した。

5.5 検査方法

1) 一般状態の観察

全例について、投与期間中は毎日、投与前および投与後に一般状態を観察した。また、剖検日は搬出前に観察した。

2) 体重測定

全例について、投与初日(投与第1日)の投与前に体重を測定し、以後毎週1回の頻度で全例の体重を測定した。また、投与期間終了日、剖検日(剖検前に18～24時間絶食)ならびに切迫屠殺時にも体重を測定した。

3) 摂餌量測定

全例について、毎週1回の頻度で、それぞれの週の第1日から第2日にかけての1日あたりの摂餌量を測定した。

4) 眼科学的検査

投与第12週に雌雄とも各群の動物番号の若いほうから順に5匹を選抜して検査した。検査は肉眼と、双眼倒像鏡(バンテージ双眼倒像鏡VA-2500型、キラー)およびスリットランプ(コーワポータブルスリットランプSL-14、興和)を用いて、前眼部、中間透光体および眼底を観察した。

5) 尿検査

投与最終週に、雌雄とも各群の動物番号の若いほうから順に5匹を選抜して代謝ケージに收容し、以下の項目について検査した。色調、濁度、試験紙による検査および尿沈渣は、代謝ケージに收容後約4時間の時点で採取した蓄尿で、その他の項目は約24時間の蓄尿で行った。また、ナトリウムイオン、カリウムイオンおよび塩素イオン濃度は、濃度に尿量を乗じて各総排泄量を算出した。

雄1例(動物番号M01004)および雌2例(動物番号F02051、F02052)のカリウムイオン濃度が初回測定時に定量範囲外となったため、蒸留水で2倍に希釈し、同測定値に希釈倍数を乗じた値を採用した。また、雌1例(動物番号F04075)の塩素イオン濃度は初回測定時に定量範囲外となったため、尿用標準液を添加して測定し、標準液値を差し引いた値を採用した。

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	メスシリンダー、ピペット
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	自動分析装置 JCA-BM6010 (日本電子)
カリウムイオン濃度	同上	同上
塩素イオン濃度	同上	同上

6) 採血

定期解剖例全例を、採血前(屠殺剖検前)に18～24時間絶食させた。その後、以下の3種混合麻酔薬による麻酔下で、腹部後大静脈より下記(1)～(4)の順序で採血した。3種混合麻酔

は塩酸メデトミジン (ドミトール、日本全薬工業)、ミダゾラム (ドルミカム注射液 10 mg、アステラス製薬) および酒石酸ブトルファノール (ベトルファール、Meiji Seika ファルマ) の混合液 (液量としてドミトールを 0.4 mL、ドルミカム注射液 10 mg を 0.4 mL、ベトルファールを 1.0 mL の割合で混合した液) を調製し、25G 注射針を用いて背部肩甲骨間の皮下に投与 (2.0 mL/kg) した。採血は可能な限り対照群、低、中および高用量群の順に各群 1 匹ずつ、動物番号の若いほうから順に選抜して行った。

- (1) 血液学的検査用採血 (抗凝固剤: EDTA 2K)
- (2) 血液学的検査用採血 (抗凝固剤: クエン酸ナトリウム)
- (3) 血液生化学的検査用採血 (抗凝固剤: なし)
- (4) 血液生化学的検査用採血 (抗凝固剤: ヘパリン)

7) 血液学的検査

前述の 6) 採血の項の (1) で採取した血液を用い、以下の項目について検査した。ただし、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は、6) 採血の項の (2) で採取した血液から血漿を分離して測定に用いた。

以下に、測定項目、測定法および使用機器名を示した。

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)	半導体レーザー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
ヘマトクリット値 (HCT)	電気抵抗検出法	同上
血小板数 (PLT)	同上	同上
平均赤血球容積 (MCV)	計算 (HCT×1000/RBC)	同上
平均赤血球血色素量 (MCH)	計算 (HGB×1000/RBC)	同上
平均赤血球血色素濃度 (MCHC)	計算 (HGB×100/HCT)	同上
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装置 CA-650 (シスメックス)
プロトロンビン時間 (PT)	同上	同上

8) 血液生化学的検査

前述の 6) 採血の項の (4) で採取した血液から血漿を分離し、以下の項目について検査した。また、6) 採血の項の (3) で採取した血液は血清を分離し、血清蛋白分画の測定用として凍結保存 (-70°C 以下) した。検査の結果、総蛋白濃度およびアルブミン濃度に被験物質投与の影響は認められなかったことから、血清蛋白分画の測定は必要がないと判断した。

以下に、測定項目、測定法および使用機器名を示した。

項目	測定法	使用機器
総蛋白濃度 (TP)	ビウレット法	自動分析装置 JCA-BM6010 (日本電子)
アルブミン濃度 (rALB)	BCG 法	同上
A/G 比 (rA/G)	計算 (rALB/(TP-rALB))	同上
グルコース濃度 (Glc)	ヘキソキナーゼ・G-6-PDH 法	同上
総コレステロール濃度 (TC)	コレステロールオキシダーゼ・HMMPS 法	同上
トリグリセライド濃度 (TG)	GPO・HMMPS 法、グリセリン消去法	同上
尿素窒素濃度 (BUN)	ウレアーゼ・GODH 法、アンモニア消去法	同上
クレアチニン濃度 (cre)	クレアチニナーゼ・HMMPS 法	同上
γ-グルタミルトランスペプチターゼ活性 (γ-GTP)	IFCC 法	同上

項目	測定法	使用機器
アルカリフォスファターゼ活性 (ALP)	GSCC 法	自動分析装置 JCA-BM6010 (日本電子)
アスパラギン酸アミノトランスフェラーゼ活性 (AST)	IFCC 法	同上
アラニンアミノトランスフェラーゼ活性 (ALT)	同上	同上
カルシウム濃度 (Ca)	OCPC 法	同上
総ビリルビン濃度 (tbil)	酵素法	同上
無機リン濃度 (IP)	モリブデン酸直接法	同上
ナトリウムイオン濃度 (Na)	イオン電極法	同上
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

9) 病理学的検査

(1) 剖検および器官重量の測定

全例を麻酔下で採血後に放血致死により安楽死させた後、剖検し、器官・組織を肉眼的に観察した。また、以下の器官の重量を測定し、併せて各器官の体重に対する相対重量も算出した。途中屠殺例は速やかに剖検し、器官・組織の肉眼的観察を実施した。

重量測定器官：脳、下垂体、顎下腺および舌下腺、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、精巣、前立腺 (腹側葉)、精嚢および凝固腺、卵巣、子宮

(2) 病理組織学的検査

切迫屠殺例 (動物番号 F04071) を含む全例について解剖時に以下の器官・組織を採取し、精巣ならびに精巣上体はブアン液 (保存は 10% 中性緩衝ホルマリン溶液) で、その他の器官・組織は 10% 中性緩衝ホルマリン溶液に固定した。対照群および高用量群について、採取した器官・組織のヘマトキシリン・エオジン染色 (HE 染色) 標本を作製し、病理組織学的検査を実施した。低および中用量群についても、肉眼的に異常が認められた器官、高用量群で被験物質投与との関連が示唆された器官・組織 (肝臓、腎臓、精巣および精巣上体) について全例の病理組織学的検査を実施した。

固定器官・組織：脳、脊髄、下垂体、眼球 (ハーダー腺)、視神経、鼻腔 (鼻甲介)、外耳道腺 (ジンバル腺)、顎下腺および舌下腺、舌、食道、気管、大動脈、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、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、顎下リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺 (腹側葉)、精嚢および凝固腺、卵巣、卵管、子宮、膣、膀胱、大腿骨および大腿骨骨髓、胸骨および胸骨骨髓、骨格筋、坐骨神経、皮膚、乳腺、病変部

5.6 データの解析法

体重、摂餌量、尿検査値 (尿量、比重、尿中電解質)、血液学的検査値、血液生化学的検査値および器官重量は、群ごとに平均値および標準偏差を求めた後、対照群と被験物質投与群との間の平均値の差を検定した。まず、Bartlett の方法により分散の一様性について検定を行った。分散が一様であった場合には一元配置型の分散分析を行い、群間に有意性が認められた場合は、Dunnnett 法により多重比較を行った。一方、分散が一様でなかった場合は Kruskal-Wallis の順位検定を行い、群間に有意性が認められた場合には、ノンパラメトリックによる Dunnnett 型の検定法で多重比較を行った。ただし、いずれかの群で分散が 0 となった場合には、Bartlett の検定は行わずに Kruskal-Wallis の順位検定を行い、以下同様に多重比較を行った。なお、いずれの場合も有意水準は 5% とした。

病理組織学的所見については、グレード分けしたデータは 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、対照群と被験物質投与群との間の有意差検定を行った (有意水準：5%)。

6. 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

本試験期間中に「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。

7. 試験成績

7.1 一般状態 (Table 1, Appendix 1)

投与期間中、300 mg/kg 投与群の雌 1 例 (動物番号 F04071) の一般状態が悪化したため、投与第 45 日に切迫屠殺した。同例では投与第 43 日から半眼、第 44 日から排便量が減少し、第 45 日の投与前に消瘦が認められた。同日の投与後にはこれらの所見に加えて腹臥位、体温低下、自発運動の消失、死戦期呼吸、無便および無尿が認められたため、同日中に安楽死させた。その他、いずれの群においても投与期間中に死亡および切迫屠殺例はみられなかつた。

300 mg/kg 投与群の生存例では、投与後の一過性の流涎が同群の雌雄で投与第 57 日から投与期間中を通して散見された。また、排便量の減少が同群の雌 1 例 (動物番号 F04075) で投与第 71～72 日に、赤色尿が同群の雌雄各 1 例 (動物番号 M04035、F04080) でそれぞれ投与第 87 日のみあるいは第 78～90 日の間に 7 日間観察された。

12 および 60 mg/kg 投与群では、一般状態の異常は観察されなかつた。

7.2 体重 (Table 2, Appendix 2)

各被験物質投与群の体重は対照群と比較して有意な差は認められなかつた。

切迫屠殺した 300 mg/kg 投与群の雌 1 例 (動物番号 F04071) の体重は投与第 36 日 (216.9 g) までは順調に増加したが、投与第 43 日の体重は 200.5 g に減少し、屠殺時体重 (投与第 45 日) は 170.2 g まで減少した。また、排便量の減少がみられた雌 1 例 (動物番号 F04075) では投与第 71 日および第 91 日の体重が前週に比較してそれぞれ 12.6 g あるいは 11.0 g 減少した。

7.3 摂餌量 (Table 3, Appendix 3)

対照群に比較して統計学的に有意な摂餌量の減少が 300 mg/kg 投与群の雌で投与第 1 日に認められた。一方、摂餌量の有意な増加が 300 mg/kg 投与群の雄で投与第 29 および 36 日にみられた。

切迫屠殺した 300 mg/kg 投与群の雌 1 例 (動物番号 F04071) の摂餌量は投与第 43 日に 0.4 g と摂餌がみられなかつた。また、排便量の減少がみられた雌 1 例 (動物番号 F04075) では投与第 36～71 日および第 85 日の摂餌量が他の例に比較して少ない傾向がみられた。

12 および 60 mg/kg 投与群では対照群との間の摂餌量に有意な差は認められなかつた。

7.4 眼科学的検査 (Table 4, Appendix 4)

雄では水晶体前極の限局性の混濁が 300 mg/kg 投与群の 1 例に、水晶体の核混濁が 12 mg/kg 投与群の 1 例に認められた。雌では水晶体前極の限局性の混濁が 300 mg/kg 投与群の 3 例に、眼底の帯状の反射性亢進が 12 mg/kg 投与群の 1 例に、眼底の網膜ひだが対照群の 1 例に認められた。また、各群の雌雄に角膜の帯状混濁が認められた。

これらの所見はいずれも自然発生性の所見と考えられた。

7.5 尿検査 (Table 5, Appendix 5)

300 mg/kg 投与群の雄 1 例 (動物番号 M04035) で尿潜血反応が認められ、尿沈渣中に赤血球が観察された。また、雌雄ともに尿量の増加、尿比重、尿中カリウムおよび塩素イオン濃度の減少が、雌では尿中ナトリウムイオン濃度の減少がいずれも対照群に比較して統計学的に有意に認められたほか、雄では尿中ナトリウム、カリウムおよび塩素イオン総排泄量の増加がいずれも有意に認められた。尿比重、ナトリウム、カリウムおよび塩素イオン濃度の減少は 60 mg/kg 投与群の雌でも有意に認められた。12 mg/kg 投与群の雄では塩素イオン総排泄量の有意な増加が認められたが、60 mg/kg 投与群では変化はみられなかつたことから、被験物質投与との関連はないと考えられた。

なお、対照群の雄 1 例では尿潜血反応が軽度に認められたが、尿沈渣中に赤血球は観察されな

かった。

7.6 血液学的検査 (Table 6, Appendix 6)

300 mg/kg 投与群の雄では、血色素量、ヘマトクリット値、MCH および MCHC の減少が、雌では血小板数および網状赤血球比率の減少、活性化部分トロンボプラスチン時間の短縮がいずれも対照群と比較して統計学的に有意に認められた。300 mg/kg 投与群の雌 1 例 (動物番号 F04080) では、他の動物に比べて赤血球数、血色素量およびヘマトクリット値が低く、網状赤血球比率が高い傾向がみられた。

血小板数の減少は 60 mg/kg 投与群の雌でも有意に認められた。

12 mg/kg 投与群では雌雄とも対照群との間に有意な差は認められなかった。

7.7 血液生化学的検査 (Table 7, Appendix 7)

300 mg/kg 投与群の雌雄では尿素窒素濃度の増加および塩素イオン濃度の減少がいずれも対照群と比較して統計学的に有意に認められた。また、同群の雄では、グルコース濃度の増加、AST および ALT 活性の上昇、トリグリセライド濃度の減少が、雌では γ -GTP 活性の上昇が有意に認められた。

グルコース濃度の増加は 60 mg/kg 投与群の雄、 γ -GTP 活性の上昇は同群の雌でも有意に認められた。

12 mg/kg 投与群では雌雄とも対照群との間に有意な差は認められなかった。

7.8 器官重量 (Table 8, Appendix 8)

300 mg/kg 投与群の雌雄では、肝臓の実重量および相対重量の増加、腎臓の相対重量の増加、顎下腺の実重量の減少がいずれも対照群と比較して統計学的に有意に認められた。また、同群の雄では腎臓の実重量の増加、精巣および精囊の実重量および相対重量の減少、雌では解剖時体重の減少、卵巣の実重量および相対重量の増加がいずれも有意に認められた。肝臓重量の増加は 60 mg/kg 投与群の雄 (相対重量) および雌 (実重量および相対重量) でも認められた。

また、下垂体の実重量の減少および脳の相対重量の増加が 300 mg/kg 投与群の雌で、脳の実重量の減少が 12、60 および 300 mg/kg 投与群の雄で認められた。

7.9 剖検所見 (Table 9, Appendix 9)

1) 切迫屠殺例

雌の 300 mg/kg 投与群の 1 例 (動物番号 F04071) を投与第 45 日に一般状態の悪化により屠殺剖検した。

剖検の結果、外観では削瘦および下腹部被毛の汚れが認められた。肝臓では小葉構造明瞭化を伴う大型化が、脾臓では小型化が、副腎では大型化がみられたほか、胸腺では小型化が認められた。その他、空腸および回腸に暗赤色斑がみられ、胃ではガスが貯留していた。

2) 投与期間終了時剖検例

被験物質投与に起因すると考えられる変化が認められた器官・組織 (肝臓、腎臓、精巣および精巣上部) の肉眼所見を次表に示した。

Text table 1 被験物質投与に起因すると考えられる変化が認められた器官・組織の肉眼所見

器官・組織、所見	性	雄				雌			
		0	12	60	300	0	12	60	300
肝臓									
大型化		0	0	0	4	0	0	0	0
暗色化		0	0	0	1	0	0	1	1
白色斑		0	0	1	0	0	0	1	0
白色結節		1	0	0	0	0	0	0	0
横隔膜結節		0	0	0	0	0	0	1	0

器官・組織、所見	性 投与用量 (mg/kg)	雄				雌			
		0	12	60	300	0	12	60	300
腎臓									
大型化		0	0	1	3	0	0	0	0
白色斑		0	0	0	1	0	0	0	0
嚢胞		0	0	0	0	1	0	0	0
精巣									
小型化		1	0	1	10				
水腫様		1	0	1	7				
精巣上部									
小型化		1	0	0	5				
黄白色結節		0	0	0	1				

数値は動物数を示す。動物数 10 匹/群。ただし、300 mg/kg 投与群の雌は 9 匹/群。

その他の所見を以下に示し、対応する組織所見を括弧内に記載した。

- ・ 肺
 - 暗赤色化：雄 対照群、M01008 (肺水腫)
 - 退縮不全：雄 12 mg/kg 投与群、M02015 (変化なし)
 - 暗赤色斑/点：雌 12 mg/kg 投与群、F02058 (限局性の出血および肺水腫)
- ・ 脾臓
 - 陥凹部：雄 300 mg/kg 投与群、M04035 (被膜に限局性の線維化)
 - 小型化：
 - 雌 60 mg/kg 投与群、F03061 (対応所見なし)
 - 雌 300 mg/kg 投与群、F04075 (対応所見なし)
- ・ 胃
 - 腺胃粘膜の黒色付着物：
 - 雄 300 mg/kg 投与群、M04035 (変化なし)
 - 雌 300 mg/kg 投与群、F04072 (変化なし)
 - 腺胃粘膜の赤色斑：雌 60 mg/kg 投与群、F03066 (限局性のうっ血)
- ・ 脂肪組織、右側の精索周囲
 - 黄色結節：雄 対照群、M01008 (線維化および単核細胞浸潤を伴う限局性脂肪壊死)

7.10 病理組織学的検査所見 (Table 10、Appendix 10、Photo 1～Photo 8)

1) 切迫屠殺例 (動物番号 F04071)

肝臓では、肝細胞がびまん性に肥大し、門脈周囲から小葉中間帯の肝細胞に細胞質空胞化がみられたほか、肝細胞の単細胞壊死が小葉中心性に認められた。

腎臓の乳頭部では、うっ血および好中球浸潤を伴う乳頭壊死が先端部に、硝子滴が乳頭上皮および乳頭管にみられたほか、尿細管の再生が認められた。また、細胞質空胞化が皮質から髓質内層の外側領域の尿細管上皮細胞に、びまん性の拡張が皮質の遠位尿細管および集合管に、鉍質沈着が髓質に認められた。その他、慢性進行性腎症が認められた。

脾臓では、白脾髄および赤脾髄ともに顕著な萎縮がみられたほか、褐色色素沈着が認められた。

胸腺、顎下リンパ節および腸間膜リンパ節では、萎縮がみられ、回腸のパイエル板ではリンパ球壊死が認められた。

大腿骨骨髓では限局性壊死が骨幹端領域に認められた。

肝臓を除く消化器系器官・組織では、肥大およびびまん性単細胞壊死が顎下腺の腺房細胞に、

チモーゲン顆粒の減少が膵臓に、細胞質の微細空胞化が腺胃の壁細胞に、杯細胞の粘液減少が結腸に認められた。その他、空腸および回腸では限局性の自己融解が認められた。

副腎では微細空胞のびまん性の増加が皮質細胞に認められた。

ハーダー腺ではポルフィリン分泌増加が認められた。

その他、心臓および肺に所見が認められた。

なお、上皮小体は、組織切片上に組織がなかったため、評価できなかった。

2) 投与期間終了時剖検例

被験物質投与に起因すると考えられる組織所見を次表に示した。

肝臓では、好酸性変化を伴う小葉中心性の肝細胞肥大が雌雄の 60 および 300 mg/kg 投与群に認められた。この内、雄の 60 mg/kg 投与群では発生頻度が雌雄の 300 mg/kg 投与群では発生頻度および変化の程度が対照群と比較して有意な増強が認められた。また、小葉中心性の肝細胞の単細胞壊死が雄の全群ならびに雌の 60 および 300 mg/kg 投与群にみられ、雌雄の 300 mg/kg 投与群において発生頻度および変化の程度ともに有意な増強が認められた。一方、門脈周囲性の肝細胞の脂肪化が雄の対照群、12 および 60 mg/kg 投与群ならびに雌の全群にみられ、雄の 60 mg/kg 投与群では変化の程度に、300 mg/kg 投与群では発生頻度および変化の程度に有意な減弱が認められた。その他、クッパー細胞の褐色色素沈着が雄の 300 mg/kg 投与群および雌の 60 および 300 mg/kg 投与群に認められた。

腎臓では、腎乳頭壊死および髄質内層の外側領域を主とした集合管の細胞質空胞化が雌雄の 300 mg/kg 投与群に、腎乳頭先端部のうっ血が雄の 12 から 300 mg/kg 投与群ならびに雌の 300 mg/kg 投与群に、皮質部遠位尿細管のびまん性の尿細管拡張が雌雄全群に認められた。この内、いずれの所見も雌雄の 300 mg/kg 投与群において発生頻度および変化の程度ともに有意な増強が認められた。また、腎乳頭上皮/乳頭管の硝子滴が雌雄の 60 および 300 mg/kg 投与群にみられ、雌雄の 300 mg/kg 投与群において発生頻度に有意な増加が認められた。その他、腎乳頭先端部の好中球浸潤および腎乳頭部の尿細管の再生が 300 mg/kg 投与群に認められた。

精巣では、精細管の変性/萎縮、ライディッヒ細胞のびまん性過形成および間質の水腫が対照群、60 および 300 mg/kg 投与群にみられ、300 mg/kg 投与群において発生頻度および変化の程度ともに有意な増強が認められた。

精巣上体では、管腔の精子減少および細胞残屑が対照群、60 および 300 mg/kg 投与群にみられ、300 mg/kg 投与群において発生頻度および変化の程度ともに有意な増強が認められた。

その他、精囊では萎縮が 300 mg/kg 投与群の 2 例にみられたが、上皮に組織学的な異常は認められなかった。

Text table 2 被験物質投与に起因すると考えられる組織所見

器官・組織、所見	性 投与用量 (mg/kg)	雄				雌			
		0	12	60	300	0	12	60	300
肝臓									
小葉中心性の肝細胞肥大	0	0	4 [#]	10 ^{**,#}	0	0	3	9 ^{**,#}	
肝細胞の単細胞壊死	1	1	5	10 ^{**,#}	0	0	2	8 ^{**,#}	
門脈周囲性の肝細胞脂肪化	10	10	8 ^{**}	0 ^{**,#}	8	6	7	6	
褐色色素沈着 (クッパー細胞)	0	0	0	3	0	0	2	2	
腎臓									
腎乳頭壊死	0	0	0	7 ^{**,#}	0	0	0	8 ^{**,#}	
うっ血 (腎乳頭先端)	0	1	1	9 ^{**,#}	0	0	0	6 ^{*,##}	
細胞質空胞化 (集合管、主に髄質内層の外側領域)	0	0	0	10 ^{**,#}	0	0	0	9 ^{**,#}	

器官・組織、所見	性 投与用量 (mg/kg)	雄				雌			
		0	12	60	300	0	12	60	300
腎臓									
尿細管拡張 (皮質部遠位尿細管、びまん性)		3	3	6	10 ^{**,#}	2	2	1	7 ^{*,#}
硝子滴 (腎乳頭上皮/乳頭管)		0	0	1	5 [#]	0	0	2	4 [#]
好中球浸潤 (腎乳頭先端)		0	0	0	3	0	0	0	2
尿細管の再生 (腎乳頭)		0	0	0	1	0	0	0	3
精巣									
精細管の変性/萎縮		2	0	2	10 ^{**,#}				
ライディッヒ細胞過形成 (びまん性)		1	0	1	10 ^{**,#}				
間質の水腫		1	0	1	10 ^{**,#}				
精巣上部									
管腔の精子減少		1	0	1	10 ^{**,#}				
管腔の細胞残屑		2	0	1	10 ^{**,#}				

数値は動物数を示す。動物数 10 匹/群。ただし、300 mg/kg 投与群の雌は 9 匹/群。

* P<0.05, ** 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's exact test).

雌雄の肝臓および腎臓ならびに精巣および精巣上部では、被験物質投与群において上記以外の自然発生性の所見が認められたが、対照群との間に発生頻度および変化の程度ともに差は認められなかった。

また、300 mg/kg 投与群の雄では、下垂体、眼球、ハーダー腺、鼻腔、甲状腺、胸腺、心臓、肺、脾臓、胃および前立腺に、雌では下垂体、眼球、ハーダー腺、鼻腔、甲状腺、胸腺、肺、脾臓、膵臓、副腎、卵巣、子宮、膣、大腿骨、大腿骨骨髓、胸骨および胸骨骨髓に所見が認められたが、いずれの所見も対照群との間に発生頻度および変化の程度ともに有意な差は認められなかった。

その他、対照群の雄では胃に、雌では顎下腺、心臓に所見が認められた。

なお、雌雄各 1 例 (M04036、F04074) では組織切片上に上皮小体がなかったため、評価できなかった。

8. 考察

指定添加物である *p*-サイメンをトウモロコシ油に溶解して、0、12、60 および 300 mg/kg の用量で、雌雄とも各群 10 匹の Crl:CD (SD) ラットに 90 日間反復経口投与した。

その結果、300 mg/kg 投与群の雌 1 例を投与第 45 日に切迫屠殺した。同例では投与第 43 日から半眼、第 44 日から排便量が減少し、第 45 日の投与前に消瘦が認められた。同日の投与後には腹臥位、体温低下、自発運動の消失、死戦期呼吸、無便および無尿が認められたため、同日中に安楽死させた。同例の体重は投与第 36 日までは順調に増加したが、第 43 日以降は減少し、第 43 日では摂餌は認められなかった。剖検および病理組織学的検査の結果、主に肝臓および腎臓に変化がみられており、被験物質投与の影響により状態が悪化したと考えられた。

被験物質投与による一般状態の変化として、投与後の一過性の流涎が 300 mg/kg 投与群の雌雄で散見されたほか、赤色尿が雌雄各 1 例で観察された。また、雌 1 例では一時的な排便量の減少および体重減少が認められ、摂餌量の減少が同群の雌で投与第 1 日に認められた。300 mg/kg 投与群では流涎や赤色尿、一般状態の悪化など被験物質投与の影響が認められた。

尿検査では、300 mg/kg 投与群の雄1例で尿潜血反応が認められ、尿沈渣中に赤血球が観察され、この動物では一般状態観察で赤色尿が観察された。また、同群の雌雄ともに尿量の増加、尿比重、尿中電解質濃度の減少が認められたほか、雄では尿中電解質総排泄量の増加も認められた。血液生化学的検査では尿素窒素濃度の増加および塩素イオン濃度の減少が 300 mg/kg 投与群の雌雄で認められた。また、雌雄の腎臓の相対重量の増加、雄の腎臓の実重量の増加が認められ、病理組織学的変化として、腎乳頭壊死および髄質内層の外側領域を主とした集合管の細胞質空胞化、腎乳頭先端部のうっ血、皮質部遠位尿細管のびまん性の尿細管拡張が雌雄で発生頻度および変化の程度ともに増強した。また、腎乳頭上皮/乳頭管の硝子滴、腎乳頭先端部の好中球浸潤および腎乳頭部の尿細管の再生が認められた。これらの所見から、被験物質が腎機能に影響を及ぼすことが明らかとなった。また、これらの所見のうち、尿比重、尿中電解質濃度の減少は 60 mg/kg 投与群の雌で、腎乳頭上皮/乳頭管の硝子滴が同群の雌雄でも認められた。なお、12 mg/kg 投与群の雄で塩素イオン総排泄量の有意な増加が認められたが、用量に関連した変化でなかったことから、被験物質投与との関連はないと考えられた。

血液学的検査では、血色素量、ヘマトクリット値、MCH および MCHC の減少が 300 mg/kg 投与群の雄で、網状赤血球比率の減少が同群の雌で認められた。また、血小板数の減少が 60 および 300 mg/kg 投与群の雌でみられており、病理組織学検査では大腿骨および胸骨骨髓の造血減少が 1 例で観察されたことから、被験物質投与による造血機能への影響が疑われた。一方で、一般状態で赤色尿が観察された雌 1 例では赤血球数、血色素量およびヘマトクリット値が減少し、網状赤血球比率は増加していたことから、泌尿器系からの出血により貧血が生じたと考えられた。なお、300 mg/kg 投与群の雌でみられた活性化部分トロンボプラスチン時間の短縮は秦野研究所背景値の 2SD 内 (14.9 sec, SD:4.0) であったことから被験物質投与との関連はないと判断した。

血液生化学的検査では、前述した尿素窒素濃度の増加および塩素イオン濃度の減少のほかに、300 mg/kg 投与群の雄で、AST および ALT 活性の上昇、雌では γ -GTP 活性の上昇が認められた。肝臓の実重量および相対重量が増加し、肝臓の病理組織学的検査では、好酸性変化を伴う小葉中心性の肝細胞肥大が雌雄の 60 および 300 mg/kg 投与群に認められたほか、小葉中心性の肝細胞の単細胞壊死が 300 mg/kg 投与群の雌雄において発生頻度および変化の程度ともに有意な増強を示した。また、門脈周囲性の肝細胞の脂肪化が 60 および 300 mg/kg 投与群の雄で有意な減弱が認められたほか、クッパー細胞の褐色色素沈着が雄の 300 mg/kg 投与群および雌の 60 および 300 mg/kg 投与群で認められた。被験物質投与により肝臓での酵素誘導が生じているほか、肝細胞の壊死や血中トランスアミナーゼの増加がみられたことから、肝障害が生じていることが明らかとなった。なお、肝臓の実重量および相対重量の増加および γ -GTP 活性の上昇は 60 mg/kg 投与群でも認められた。

また、血液生化学的検査では、60 および 300 mg/kg 投与群の雄でグルコース濃度が増加し、300 mg/kg 投与群の雄でトリグリセライド濃度の減少が認められた。Triton WR1339 誘発性の高脂血症を発症したラットに、*p*-サイメンと同じモノテルペンである γ -テルピネン 100 mg/kg BW を 3 日間経口投与すると血清総コレステロールおよびトリグリセライド濃度が下がるとの報告がある¹⁾。*p*-サイメンも同様に脂質代謝に影響を及ぼすと考えられた。一方、糖代謝に及ぼす原因は明らかにできなかった。

器官重量では、前述した腎臓および肝臓重量の増加のほかに、同群の雄では精巣および精囊の実重量および相対重量が減少し、病理組織学的検査では、精細管の変性/萎縮、ライディッヒ細胞のびまん性過形成および間質の水腫が 300 mg/kg 投与群において発生頻度および変化の程度ともに増強が認められた。精巣上体では、管腔の精子減少および細胞残屑が 300 mg/kg 投与群において発生頻度および変化の程度ともに有意な増強が認められた。精囊では萎縮が認められた。また、300 mg/kg 投与群の雌では卵巣の実重量および相対重量の増加が有意に認められた。被験物質が雌雄の生殖器に影響を及ぼし、精子形成の低下を来すことが明らかとなったが、その発生機序は明らかにできなかった。下垂体の実重量の減少が 300 mg/kg 投与群の雌で認められた。下垂体の病理組織学的所見に異常は認められなかったものの同群の 1 例で秦野研究所背景値の 2SD (平均: 15.1 mg, SD: 3.6) よりも低値を示したことから、被験物質が下垂体に影響を及ぼしている可能性が考えられた。脳の実重量の減少が 12、60 および 300 mg/kg 投与群の雄で認められた。脳の病理組織学的所見に異常は認められなかったものの、全投与用量群で認められており、原因は不明であるが被験物質投与の影響と考えられた。

なお、脳の相対重量の増加が 300 mg/kg 投与群の雌でみられたが、解剖時体重が対照群に比較して低下していたことによる変化と考えられた。また、顎下腺の実重量の減少が 300 mg/kg 投与群の雌雄で認められたが、秦野研究所背景値のほぼ 2SD 内 (雄平均 : 749.5 mg、SD : 101.7、雌平均 : 424.7 mg、SD : 42.9) であり、顎下腺の病理組織学的所見に異常は認められなかったことから被験物質投与との関連はないと判断した。

その他、摂餌量の増加が 300 mg/kg 投与群の雄で投与第 29 および 36 日のみに認められたが、この前後の週の摂餌量に変化はみられなかったことから、被験物質投与との関連はないと考えられた。また、眼科学的検査では、自然発生性の所見が散見された。

以上の結果から、*p*-サイメン投与による影響として、300 mg/kg 投与群では 1 例を切迫屠殺し、造血機能、肝臓、腎臓および精巣への影響が認められた。肝臓および腎臓の変化は 60 mg/kg 投与群の雌雄でもみられた。また、脳の実重量の減少が 12、60 および 300 mg/kg 投与群の雄で認められたことから、本試験条件下における *p*-サイメンの無毒性量は、雄では 12 mg/kg/day 未満、雌では 12 mg/kg/day と考えられた。

9. 参考文献

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Table 1
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
General condition of males

Group	Number of males and general conditions	Days of administration																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		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
Control (vehicle: corn oil)	Number of males	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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	
	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

Group	Number of males and general conditions	Days of administration																											
		15		16		17		18		19		20		21		22		23		24		25		26		27		28	
		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
Control (vehicle: corn oil)	Number of males	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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
	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

Group	Number of males and general conditions	Days of administration																											
		29		30		31		32		33		34		35		36		37		38		39		40		41		42	
		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
Control (vehicle: corn oil)	Number of males	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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
	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

Pre: Before administration, Post: after administration.

Table 1 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 General condition of males

Group	Number of males and general conditions	Days of administration																																			
		43		44		45		46		47		48		49		50		51		52		53		54		55		56									
		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						
Control (vehicle: corn oil)	Number of males	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		
	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	10	10	10	10	10	10	10	
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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	
	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	10	10	10	10	10	10	10	10
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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	
	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	10	10	10	10	10	10	10	10
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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	
	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	10	10	10	10	10	10	10	10

Group	Number of males and general conditions	Days of administration																																			
		57		58		59		60		61		62		63		64		65		66		67		68		69		70									
		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		
Control (vehicle: corn oil)	Number of males	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	
	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	10	10	10	10	10	10	10	10
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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
	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	10	10	10	10	10	10	10	10
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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
	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	10	10	10	10	10	10	10	10
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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	
	General appearance, No abnormality	10	5	10	5	10	5	10	8	10	6	10	4	10	5	10	7	10	3	10	4	10	8	10	6	10	6	10	6	10	5	10	5	10	5		
	Mouth, Salivation	0	5	0	5	0	5	0	2	0	4	0	6	0	5	0	3	0	7	0	6	0	2	0	4	0	4	0	4	0	5	0	5	0	5		

Group	Number of males and general conditions	Days of administration																																									
		71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91	
		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	Pre	Post	Pre	Post	Pre	Post		
Control (vehicle: corn oil)	Number of males	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		
	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	10	10	10	10	10	10	10	10	10	10	10	10	10	
Low dose (<i>p</i> -Cymene 12 mg/kg)	Number of males	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		
	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	10	10	10	10	10	10	10	10	10	10	10	10		
Medium dose (<i>p</i> -Cymene 60 mg/kg)	Number of males	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		
	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	10	10	10	10	10	10	10	10	10	10	10	10		
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of males	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			
	General appearance, No abnormality	10	6	10	6	10	5	10	3	10	4	10	5	10	4	10	5	10	6	10	7	10	8	10	7	10	2	10	7	10	6	9	4	10	5	10	5	10	5	10			
	Mouth, Salivation	0	4	0	4	0	5	0	7	0	6	0	5	0	6	0	5	0	4	0	3	0	2	0	3	0	8	0	8	0	3	0	4	0	6	0	5	0	5	0			
	Excretion, Reddish urine	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	0	0	0	0	0	0	0	0	0	0	0	0			

Pre: Before administration, Post: after administration.

Table 1 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 General condition of females

Group	Number of females and general conditions	Days of administration																											
		1		2		3		4		5		6		7		8		9		10		11		12		13		14	
		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
Control (vehicle: corn oil)	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	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	
	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

Group	Number of females and general conditions	Days of administration																											
		15		16		17		18		19		20		21		22		23		24		25		26		27		28	
		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
Control (vehicle: corn oil)	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	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	
	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

Group	Number of females and general conditions	Days of administration																											
		29		30		31		32		33		34		35		36		37		38		39		40		41		42	
		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
Control (vehicle: corn oil)	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	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	
	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

Pre: Before administration, Post: after administration.

Table 1 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 General condition of females

Group	Number of females and general conditions	Days of administration																											
		43		44		45		46		47		48		49		50		51		52		53		54		55		56	
		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
Control (vehicle: corn oil)	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of females	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	General appearance, No abnormality	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	Excretion, Decrease in amount of feces	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	General appearance, Emaciation	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Anuria	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Posture, Body position, Prone position	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Body temperature, Hypothermia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Behavior, Loss of locomotor activity	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Breathing, Agonal respiration	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Excretion, No-feces	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Group	Number of females and general conditions	Days of administration																											
		57		58		59		60		61		62		63		64		65		66		67		68		69		70	
		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
Control (vehicle: corn oil)	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	
	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
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	General appearance, No abnormality	9	7	9	6	9	7	9	7	9	7	9	6	9	6	9	5	9	6	9	6	9	6	9	6	9	6	9	6
	Mouth, Salivation	0	2	0	3	0	2	0	2	0	2	0	3	0	3	0	4	0	3	0	3	0	3	0	3	0	3	0	3

Group	Number of females and general conditions	Days of administration																																											
		71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91		92	
		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	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control (vehicle: corn oil)	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		
	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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Low dose (<i>p</i> -Cymene 12 mg/kg)	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	
	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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Medium dose (<i>p</i> -Cymene 60 mg/kg)	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	
	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	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
High dose (<i>p</i> -Cymene 300 mg/kg)	Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9		
	General appearance, No abnormality	8	6	8	7	9	6	9	5	9	6	9	5	9	5	9	6	9	6	9	7	9	4	9	4	9	7	9	7	8	7	8	7	8	7	9	6	9	6	9	7	9			
	Mouth, Salivation	0	2	0	2	0	3	0	4	0	4	0	3	0	4	0	4	0	3	0	2	0	2	0	5	0	5	0	2	0	2	0	2	0	3	0	3	0	3	0	2	0			
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0			
	Excretion, Decrease in amount of feces	1	1	1	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	0	0	0	0	0	0	0	0	0	0	0	0		

Pre: Before administration, Post: after administration.

Table 2
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Body weight of males

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of males	10	10	10	10
Days of administration				
1	134.4 ± 4.8	134.6 ± 5.5	132.4 ± 6.0	135.2 ± 5.2
8	194.2 ± 9.7	191.1 ± 11.7	193.8 ± 13.5	195.8 ± 11.6
15	247.1 ± 17.1	243.0 ± 17.2	245.2 ± 18.3	247.1 ± 15.0
22	300.2 ± 23.2	296.3 ± 19.6	298.7 ± 25.4	300.3 ± 17.0
29	346.6 ± 29.7	343.0 ± 23.2	345.4 ± 29.0	344.6 ± 18.5
36	386.0 ± 38.3	382.3 ± 27.6	380.2 ± 30.7	379.3 ± 22.0
43	417.1 ± 43.1	415.1 ± 34.2	413.2 ± 35.1	407.4 ± 22.9
50	444.2 ± 48.1	442.6 ± 38.7	437.0 ± 37.4	429.8 ± 26.5
57	469.4 ± 50.5	468.6 ± 44.9	460.9 ± 39.6	454.3 ± 24.7
64	491.4 ± 53.1	486.9 ± 48.5	479.1 ± 43.1	471.2 ± 27.0
71	508.1 ± 55.7	506.1 ± 54.0	495.0 ± 45.2	487.0 ± 28.7
78	526.2 ± 57.6	525.0 ± 56.1	512.7 ± 46.0	499.3 ± 32.2
85	543.0 ± 57.4	542.6 ± 59.6	528.4 ± 47.4	510.2 ± 35.2
90	549.1 ± 58.8	550.1 ± 60.7	539.1 ± 50.5	514.4 ± 36.2

Each value shows mean (g) ± S.D.

Table 2 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Body weight of females

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of females	10	10	10	10
Days of administration				
1	129.7 ± 4.8	130.4 ± 4.5	129.8 ± 4.9	128.8 ± 4.5
8	159.1 ± 9.7	160.9 ± 6.1	162.3 ± 11.3	157.9 ± 9.7
15	175.5 ± 11.8	175.9 ± 9.3	179.3 ± 12.4	170.9 ± 15.3
22	198.8 ± 13.1	195.2 ± 11.0	201.4 ± 16.0	191.2 ± 16.1
29	217.3 ± 14.0	214.0 ± 13.5	218.1 ± 18.7	208.4 ± 19.4
36	228.6 ± 14.5	231.1 ± 18.3	231.6 ± 25.1	223.1 ± 21.3
43	241.6 ± 16.7	240.9 ± 18.6	244.5 ± 25.1	233.8 ± 27.1
50	254.9 ± 18.8	249.5 ± 18.7	255.5 ± 26.2	244.2 ± 26.6 (9)
57	266.4 ± 18.4	260.8 ± 16.2	265.2 ± 26.3	256.2 ± 28.2 (9)
64	273.4 ± 18.2	269.5 ± 17.1	273.8 ± 29.2	261.4 ± 29.2 (9)
71	282.3 ± 19.9	279.4 ± 18.5	284.9 ± 30.0	264.3 ± 32.0 (9)
78	291.9 ± 21.4	285.7 ± 20.6	290.9 ± 31.5	266.4 ± 31.9 (9)
85	297.2 ± 22.0	292.7 ± 19.6	295.2 ± 28.4	269.8 ± 33.4 (9)
91	300.8 ± 20.7	297.0 ± 18.3	298.3 ± 30.7	267.3 ± 32.8 * (9)

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.

Table 3
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Food consumption of males

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of males	10	10	10	10
Days of administration				
1	19.3 ± 1.3	19.7 ± 1.3	19.8 ± 0.9	18.5 ± 1.4
8	22.0 ± 2.2	21.6 ± 1.6	22.0 ± 2.4	21.7 ± 1.8
15	23.2 ± 2.0	23.0 ± 1.6	23.8 ± 2.5	23.9 ± 1.9
22	23.2 ± 3.1	23.8 ± 1.9	24.5 ± 2.0	25.9 ± 1.6
29	24.4 ± 3.0	24.9 ± 1.5	25.1 ± 2.9	27.4 ± 2.0 *
36	22.7 ± 2.9	23.5 ± 3.0	24.5 ± 2.9	26.2 ± 2.4 *
43	24.0 ± 3.6	23.6 ± 3.0	24.5 ± 2.6	25.1 ± 1.8
50	22.6 ± 3.1	24.7 ± 3.9	24.4 ± 2.7	26.0 ± 1.8
57	24.7 ± 2.7	23.9 ± 3.5	24.1 ± 2.1	25.8 ± 1.5
64	22.4 ± 2.8	23.3 ± 4.2	23.5 ± 3.3	23.3 ± 2.5
71	22.8 ± 2.8	23.2 ± 2.9	22.5 ± 2.8	24.9 ± 2.1
78	23.5 ± 3.3	24.4 ± 4.0	23.4 ± 2.5	23.3 ± 2.5
85	23.0 ± 3.1	22.2 ± 3.6	22.4 ± 2.8	24.4 ± 2.6

Each value shows mean (g) ± S.D.

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

Table 3 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Food consumption of females

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of females	10	10	10	10	
Days of administration					
1	18.7 ± 1.0	18.2 ± 1.2	17.7 ± 1.5	15.9 ± 1.6 **	
8	17.6 ± 1.3	17.4 ± 2.5	17.6 ± 2.5	17.0 ± 1.7	
15	15.3 ± 1.6	16.4 ± 1.9	16.4 ± 3.0	15.1 ± 5.6	
22	16.1 ± 2.1	15.8 ± 3.1	16.0 ± 2.5	16.3 ± 1.9	
29	17.5 ± 3.2	17.3 ± 3.3	18.2 ± 2.0	17.9 ± 2.8	
36	18.0 ± 1.8	16.9 ± 3.1	16.8 ± 2.2	18.5 ± 4.8	
43	15.4 ± 2.0	17.4 ± 2.6	16.8 ± 3.1	16.1 ± 7.2	
50	17.2 ± 2.3	16.6 ± 3.2	16.8 ± 2.8	16.8 ± 3.4	(9)
57	18.1 ± 2.7	17.0 ± 4.0	18.3 ± 2.3	17.6 ± 4.1	(9)
64	17.8 ± 2.4	17.0 ± 2.5	16.9 ± 2.9	17.6 ± 3.6	(9)
71	15.8 ± 1.9	17.6 ± 2.5	17.3 ± 3.0	17.5 ± 4.4	(9)
78	17.4 ± 2.2	19.3 ± 2.8	15.5 ± 2.8	19.5 ± 3.9	(9)
85	18.4 ± 2.2	16.2 ± 1.8	16.5 ± 2.0	16.5 ± 3.2	(9)

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.

Table 4
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Ophthalmologic examination

Males

Group	Control (vehicle: corn oil)		Low dose (p-Cymene 12 mg/kg)		Medium dose (p-Cymene 60 mg/kg)		High dose (p-Cymene 300 mg/kg)	
	-	+	-	+	-	+	-	+
Cornea								
Band-shaped opacity	3	2	2	3	2	3	1	4
Lens								
Opacity, nucleus	5	0	4	1	5	0	5	0
Opacity, anterior pole, focal	5	0	5	0	5	0	4	1

Females

Group	Control (vehicle: corn oil)		Low dose (p-Cymene 12 mg/kg)		Medium dose (p-Cymene 60 mg/kg)		High dose (p-Cymene 300 mg/kg)	
	-	+	-	+	-	+	-	+
Cornea								
Band-shaped opacity	3	2	3	2	3	2	2	3
Lens								
Opacity, anterior pole, focal	5	0	5	0	5	0	2	3
Fundus								
Retinal folds	4	1	5	0	5	0	5	0
Hyper-reflective fundus	5	0	4	1	5	0	5	0

-, not observed

+, observed

Number represent the number of animals.

Table 5
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Urinalysis of males

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of males	5	5	5	5
pH				
6.5	0	0	0	1
7.0	2	1	2	0
7.5	2	1	0	2
8.0	0	2	2	0
8.5	0	1	1	2
≥9.0	1	0	0	0
Protein				
- (negative)	0	0	0	0
± (10 ≤ and < 30 mg/dL)	0	0	0	1
+ (30 ≤ and < 100 mg/dL)	2	2	3	3
2+ (100 ≤ and < 300 mg/dL)	3	3	2	1
Glucose				
- (negative)	5	5	5	5
Ketone				
- (negative)	1	0	0	1
± (5 ≤ and < 10 mg/dL)	1	1	2	3
+ (10 ≤ and < 40 mg/dL)	3	4	3	1
Bilirubin				
- (negative)	5	5	5	5
Occult blood				
- (negative)	4	5	5	4
± (0.03 ≤ and < 0.06 mg/dL)	1	0	0	0
+ (0.06 ≤ and < 0.20 mg/dL)	0	0	0	0
2+ (0.20 ≤ and < 1.00 mg/dL)	0	0	0	1
Urobilinogen				
± (normal)	2	1	2	5
+ (2.0 ≤ and < 4.0 mg/dL)	2	3	3	0
2+ (4.0 ≤ and < 8.0 mg/dL)	1	1	0	0
Color				
light yellow	4	5	5	5
yellow	1	0	0	0
Turbidity				
- (negative)	5	5	5	4
± (trace)	0	0	0	0
+ (slight)	0	0	0	1
Red Blood cells				
- (not observed)	5	5	5	4
± (1-9/3 visual field)	0	0	0	0
+ (10-99/3 visual field)	0	0	0	0
2+ (100-299/3 visual field)	0	0	0	0
3+ (≥300/3 visual field)	0	0	0	1
White Blood cells				
- (not observed)	5	5	5	5
Casts				
- (not observed)	5	5	5	5
Crystals				
- (not observed)	1	1	1	2
± (a few)	4	4	4	3
Epithelial cells				
- (not observed)	5	5	5	5

Table 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of males

Group	Control (vehicle: corn oil)		Low dose (p-Cymene 12 mg/kg)		Medium dose (p-Cymene 60 mg/kg)		High dose (p-Cymene 300 mg/kg)	
Number of males	5		5		5		5	
Urine volume (mL/24hr)	12.0 ±	3.4	14.4 ±	2.2	18.5 ±	3.0	42.3 ±	7.7 **
Specific gravity	1.058 ±	0.011	1.055 ±	0.009	1.045 ±	0.006	1.027 ±	0.009 **
Electrolyte, density								
Na(mEq/L)	102.8 ±	39.3	117.1 ±	31.4	86.4 ±	14.2	62.4 ±	17.1
K(mEq/L)	238.74 ±	49.40	247.85 ±	37.49	193.57 ±	29.55	113.20 ±	34.23 **
Cl(mEq/L)	117.3 ±	32.5	149.5 ±	26.3	107.6 ±	16.8	69.1 ±	21.7 *
Electrolyte, gross volume								
Na(mEq/24hr)	1.21 ±	0.42	1.69 ±	0.50	1.58 ±	0.27	2.54 ±	0.24 **
K(mEq/24hr)	2.81 ±	0.69	3.56 ±	0.67	3.52 ±	0.47	4.60 ±	0.47 **
Cl(mEq/24hr)	1.42 ±	0.50	2.15 ±	0.49 *	1.96 ±	0.34	2.81 ±	0.37 **

Each value shows mean ± S.D.

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

Table 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of females

Group	Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of females	5	5	5	5
pH				
6.0	0	0	1	0
6.5	1	3	2	0
7.0	2	1	1	2
7.5	1	0	1	0
8.0	0	1	0	3
8.5	0	0	0	0
≥9.0	1	0	0	0
Protein				
- (negative)	0	1	0	1
±(10 ≤ and < 30 mg/dL)	1	1	3	4
+ (30 ≤ and < 100 mg/dL)	4	1	2	0
2+ (100 ≤ and < 300 mg/dL)	0	2	0	0
Glucose				
- (negative)	5	5	5	5
Ketone				
- (negative)	0	2	1	5
±(5 ≤ and < 10 mg/dL)	4	1	3	0
+ (10 ≤ and < 40 mg/dL)	1	2	1	0
Bilirubin				
- (negative)	5	4	5	5
+ (0.5 ≤ and < 2.0 mg/dL)	0	1	0	0
Occult blood				
- (negative)	5	5	5	5
Urobilinogen				
±(normal)	0	3	4	5
+ (2.0 ≤ and < 4.0 mg/dL)	4	1	1	0
2+ (4.0 ≤ and < 8.0 mg/dL)	1	1	0	0
Color				
light yellow	5	4	5	5
yellow	0	1	0	0
Turbidity				
- (negative)	5	5	5	5
Red Blood cells				
- (not observed)	5	5	5	5
White Blood cells				
- (not observed)	5	5	5	5
Casts				
- (not observed)	5	5	5	5
Crystals				
- (not observed)	1	2	3	3
±(a few)	4	3	2	2
Epithelial cells				
- (not observed)	5	5	5	5

Table 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of females

Group	Control (vehicle: corn oil)		Low dose (<i>p</i> -Cymene 12 mg/kg)		Medium dose (<i>p</i> -Cymene 60 mg/kg)		High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of females	5		5		5		5	
Urine volume (mL/24hr)	11.6 ± 3.1		11.1 ± 3.6		16.7 ± 3.2		27.3 ± 11.8 **	
Specific gravity	1.053 ± 0.008		1.056 ± 0.017		1.034 ± 0.006 *		1.026 ± 0.010 **	
Electrolyte, density								
Na(mEq/L)	121.0 ± 8.7		116.3 ± 32.1		71.5 ± 21.6 *		59.0 ± 27.5 **	
K(mEq/L)	245.17 ± 26.38		255.26 ± 80.16		130.79 ± 61.15 *		93.66 ± 63.81 **	
Cl(mEq/L)	150.1 ± 17.5		153.3 ± 47.1		71.4 ± 41.8 *		57.1 ± 38.5 **	
Electrolyte, gross volume								
Na(mEq/24hr)	1.39 ± 0.28		1.21 ± 0.16		1.23 ± 0.53		1.41 ± 0.55	
K(mEq/24hr)	2.79 ± 0.43		2.61 ± 0.23		2.29 ± 1.27		2.21 ± 1.38	
Cl(mEq/24hr)	1.71 ± 0.31		1.57 ± 0.13		1.27 ± 0.84		1.32 ± 0.87	

Each value shows mean ± S.D.

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

Table 6
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Hematological analysis of males

Group		Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of males		10	10	10	10	
RBC	10000/ μ L	901 \pm 61	934 \pm 63	901 \pm 56	853 \pm 59	
HGB	g/dL	16.2 \pm 1.1	16.6 \pm 1.4	16.0 \pm 1.2	14.7 \pm 0.7	*
Hematocrit	%	47.4 \pm 2.8	48.6 \pm 4.0	46.8 \pm 3.7	43.7 \pm 1.7	*
MCV	fL	52.6 \pm 1.0	52.0 \pm 2.0	52.0 \pm 2.3	51.3 \pm 1.8	
MCH	pg	18.0 \pm 0.3	17.8 \pm 0.6	17.8 \pm 0.7	17.3 \pm 0.5	*
MCHC	g/dL	34.3 \pm 0.5	34.3 \pm 0.5	34.2 \pm 0.4	33.7 \pm 0.4	**
Platelet	10000/ μ L	103.0 \pm 12.1	106.0 \pm 11.4	111.2 \pm 12.2	108.8 \pm 13.1	
PT	sec.	15.7 \pm 2.7	15.2 \pm 2.6	14.2 \pm 1.6	13.4 \pm 3.6	
APTT	sec.	16.1 \pm 2.3	16.3 \pm 2.0	15.8 \pm 2.8	14.7 \pm 1.8	
WBC	100/ μ L	117.2 \pm 25.0	92.1 \pm 31.7	97.3 \pm 24.8	111.0 \pm 36.4	
Neutrophil	%	15.4 \pm 5.1	20.1 \pm 7.4	15.6 \pm 3.3	16.9 \pm 6.5	
Eosinophil	%	1.4 \pm 0.8	1.5 \pm 0.6	1.5 \pm 0.7	0.9 \pm 0.5	
Basophil	%	0.1 \pm 0.1	0.0 \pm 0.1	0.1 \pm 0.0	0.0 \pm 0.0	
Monocyte	%	3.9 \pm 0.8	3.7 \pm 1.0	3.4 \pm 0.8	3.9 \pm 0.9	
Lymphocyte	%	79.3 \pm 5.6	74.7 \pm 8.0	79.3 \pm 3.5	78.3 \pm 6.7	
Reticulocyte	%	3.10 \pm 0.72	3.18 \pm 0.37	3.25 \pm 0.47	2.95 \pm 0.37	

Each value shows mean \pm S.D.

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

Table 6 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Hematological analysis of females

Group		Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)
Number of females		10	10	10	9
RBC	10000/ μ L	800 \pm 71	797 \pm 63	812 \pm 47	786 \pm 100
HGB	g/dL	15.0 \pm 1.2	15.0 \pm 0.9	15.1 \pm 0.6	14.5 \pm 1.7
Hematocrit	%	43.6 \pm 3.2	43.4 \pm 2.9	44.0 \pm 1.8	42.4 \pm 4.9
MCV	fL	54.6 \pm 1.5	54.6 \pm 1.9	54.3 \pm 1.5	54.1 \pm 1.5
MCH	pg	18.8 \pm 0.5	18.9 \pm 0.7	18.6 \pm 0.4	18.4 \pm 0.5
MCHC	g/dL	34.5 \pm 0.5	34.6 \pm 0.4	34.2 \pm 0.4	34.1 \pm 0.4
Platelet	10000/ μ L	104.2 \pm 8.8	94.3 \pm 8.8	86.2 \pm 12.6 **	84.5 \pm 8.3 **
PT	sec.	11.2 \pm 0.5	11.1 \pm 0.2	11.1 \pm 0.5	11.4 \pm 0.4
APTT	sec.	13.1 \pm 1.8	12.3 \pm 1.8	11.7 \pm 1.4	10.4 \pm 1.5 **
WBC	100/ μ L	63.3 \pm 15.7	63.1 \pm 7.4	63.4 \pm 24.1	67.4 \pm 12.3
Neutrophil	%	13.9 \pm 5.0	10.6 \pm 2.7	13.4 \pm 5.6	9.2 \pm 3.2
Eosinophil	%	1.8 \pm 0.5	1.5 \pm 0.5	2.0 \pm 1.2	1.4 \pm 0.6
Basophil	%	0.0 \pm 0.0	0.0 \pm 0.1	0.0 \pm 0.0	0.0 \pm 0.0
Monocyte	%	2.8 \pm 0.9	2.7 \pm 0.6	3.3 \pm 1.2	2.4 \pm 1.0
Lymphocyte	%	81.6 \pm 5.3	85.1 \pm 3.1	81.3 \pm 7.1	87.1 \pm 4.1
Reticulocyte	%	3.12 \pm 0.59	2.60 \pm 0.42	2.64 \pm 0.38	2.32 \pm 0.85 *

Each value shows mean \pm S.D.

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

Table 7
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Blood biochemical analysis of males

Group		Control (vehicle: corn oil)	Low dose (<i>p</i> -Cymene 12 mg/kg)	Medium dose (<i>p</i> -Cymene 60 mg/kg)	High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of males		10	10	10	10	
Total protein	g/dL	5.6 ± 0.4	5.6 ± 0.4	5.8 ± 0.3	5.4 ± 0.2	
Albumin	g/dL	3.5 ± 0.2	3.4 ± 0.2	3.5 ± 0.2	3.5 ± 0.2	
A/G		1.62 ± 0.12	1.57 ± 0.15	1.57 ± 0.19	1.76 ± 0.16	
Glucose	mg/dL	224 ± 34	269 ± 39	284 ± 51	296 ± 44	**
Total cholesterol	mg/dL	53 ± 10	57 ± 9	58 ± 16	51 ± 9	
Triglyceride	mg/dL	45 ± 23	46 ± 20	34 ± 16	20 ± 6	**
AST	U/L	55 ± 6	53 ± 7	61 ± 19	70 ± 13	*
ALT	U/L	26 ± 4	29 ± 4	31 ± 13	35 ± 7	**
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
BUN	mg/dL	11.7 ± 1.7	12.9 ± 2.5	13.0 ± 2.2	15.8 ± 3.1	**
Creatinine	mg/dL	0.27 ± 0.04	0.32 ± 0.17	0.31 ± 0.08	0.33 ± 0.05	
Total bilirubin	mg/dL	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	
ALP	U/L	531 ± 109	497 ± 64	545 ± 134	625 ± 174	
Inorganic phosphorus	mg/dL	7.0 ± 1.2	7.9 ± 2.6	7.8 ± 2.0	7.6 ± 1.2	
Ca	mg/dL	9.7 ± 0.6	9.9 ± 0.4	9.9 ± 0.3	9.9 ± 0.3	
Na	mEq/L	142.2 ± 1.5	140.8 ± 1.5	140.6 ± 1.9	140.5 ± 1.8	
K	mEq/L	4.16 ± 0.42	4.67 ± 0.68	4.76 ± 0.89	4.48 ± 0.54	
Cl	mEq/L	105.0 ± 2.1	104.1 ± 2.8	102.9 ± 2.4	101.3 ± 2.7	**

Each value shows mean ± S.D.

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

Table 7 (Continued)

Ninety-day repeated dose oral toxicity test of p-Cymene in rats

Blood biochemical analysis of females

Group		Control (vehicle: corn oil)	Low dose (p-Cymene 12 mg/kg)	Medium dose (p-Cymene 60 mg/kg)	High dose (p-Cymene 300 mg/kg)	
Number of females		10	10	10	9	
Total protein	g/dL	5.3 ± 0.2	5.3 ± 0.3	5.3 ± 0.3	5.0 ± 0.4	
Albumin	g/dL	3.4 ± 0.1	3.4 ± 0.2	3.4 ± 0.2	3.2 ± 0.2	
A/G		1.86 ± 0.19	1.84 ± 0.14	1.81 ± 0.21	1.89 ± 0.18	
Glucose	mg/dL	156 ± 20	138 ± 20	171 ± 24	179 ± 29	
Total cholesterol	mg/dL	55 ± 12	57 ± 8	62 ± 9	64 ± 13	
Triglyceride	mg/dL	18 ± 7	22 ± 9	19 ± 6	16 ± 7	
AST	U/L	53 ± 6	53 ± 9	56 ± 5	57 ± 8	
ALT	U/L	22 ± 4	25 ± 9	19 ± 2	20 ± 3	
γ-GTP	U/L	0 ± 0	0 ± 0	1 ± 0	2 ± 1	**
BUN	mg/dL	12.6 ± 1.9	13.7 ± 2.2	12.4 ± 2.2	20.3 ± 6.0	**
Creatinine	mg/dL	0.36 ± 0.03	0.36 ± 0.05	0.32 ± 0.04	0.40 ± 0.08	
Total bilirubin	mg/dL	0.05 ± 0.02	0.05 ± 0.01	0.05 ± 0.00	0.04 ± 0.01	
ALP	U/L	264 ± 75	319 ± 68	275 ± 58	283 ± 50	
Inorganic phosphorus	mg/dL	7.2 ± 1.8	7.0 ± 1.9	7.1 ± 1.2	7.6 ± 1.2	
Ca	mg/dL	8.6 ± 0.2	8.6 ± 0.5	8.6 ± 0.3	8.4 ± 0.3	
Na	mEq/L	140.5 ± 2.1	140.3 ± 2.4	140.0 ± 1.9	138.0 ± 3.2	
K	mEq/L	4.55 ± 0.53	4.48 ± 0.53	4.50 ± 0.52	4.56 ± 0.41	
Cl	mEq/L	104.1 ± 2.7	104.0 ± 2.1	101.9 ± 1.4	98.8 ± 4.2	**

Each value shows mean ± S.D.

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

Table 8
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Organ weight of males

Group		Control (vehicle: corn oil)		Low dose (<i>p</i> -Cymene 12 mg/kg)		Medium dose (<i>p</i> -Cymene 60 mg/kg)		High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of males		10		10		10		10	
Body weight	(g)	524.0 ±	57.3	525.1 ±	59.0	512.0 ±	49.0	481.6 ±	35.7
Brain	(mg)	2050.0 ±	90.4	1942.0 ±	75.4 **	1951.1 ±	43.5 **	1940.4 ±	54.1 **
	(mg/g)	3.955 ±	0.468	3.735 ±	0.387	3.845 ±	0.409	4.048 ±	0.305
Thymus	(mg)	273.3 ±	73.8	298.6 ±	91.2	276.2 ±	94.3	283.5 ±	74.1
	(mg/g)	0.517 ±	0.105	0.571 ±	0.176	0.535 ±	0.162	0.587 ±	0.146
Heart	(mg)	1449.9 ±	181.4	1513.6 ±	209.0	1464.0 ±	147.5	1347.4 ±	116.9
	(mg/g)	2.766 ±	0.154	2.888 ±	0.289	2.863 ±	0.190	2.800 ±	0.181
Lungs	(mg)	1647.9 ±	325.3	1676.2 ±	460.6	1589.5 ±	209.5	1553.4 ±	179.8
	(mg/g)	3.145 ±	0.511	3.231 ±	1.020	3.108 ±	0.307	3.257 ±	0.578
Liver	(mg)	14128.5 ±	2784.5	15056.3 ±	2347.4	15396.9 ±	1783.9	20275.8 ±	2254.7 **
	(mg/g)	26.833 ±	2.858	28.633 ±	2.720	30.106 ±	2.481 *	42.054 ±	2.774 **
Kidney (R)	(mg)	1656.4 ±	234.4	1754.8 ±	182.7	1775.9 ±	171.3	1939.8 ±	248.4 *
	(mg/g)	3.153 ±	0.174	3.375 ±	0.477	3.484 ±	0.346	4.020 ±	0.338 **
Kidney (L)	(mg)	1630.5 ±	219.4	1763.4 ±	184.6	1755.0 ±	183.3	1934.9 ±	262.3 **
	(mg/g)	3.105 ±	0.146	3.391 ±	0.467	3.441 ±	0.333	4.013 ±	0.413 **
Kidney	(mg)	3286.9 ±	447.3	3518.2 ±	360.8	3530.9 ±	351.8	3874.6 ±	501.8 **
	(mg/g)	6.258 ±	0.287	6.766 ±	0.935	6.925 ±	0.673	8.033 ±	0.729 **
Spleen	(mg)	819.5 ±	121.3	849.5 ±	109.8	768.6 ±	114.1	793.2 ±	111.8
	(mg/g)	1.566 ±	0.178	1.620 ±	0.129	1.504 ±	0.188	1.647 ±	0.203
Testis (R)	(mg)	1560.8 ±	246.3	1700.9 ±	166.6	1497.8 ±	306.5	811.0 ±	120.8 **
	(mg/g)	3.018 ±	0.559	3.270 ±	0.446	2.937 ±	0.658	1.681 ±	0.202 **
Testis (L)	(mg)	1639.6 ±	134.9	1834.1 ±	457.7	1480.8 ±	338.5	818.8 ±	96.0 **
	(mg/g)	3.150 ±	0.298	3.517 ±	0.869	2.895 ±	0.696	1.705 ±	0.207 **
Testis	(mg)	3200.4 ±	318.5	3535.0 ±	583.8	2978.6 ±	642.5	1629.8 ±	187.1 **
	(mg/g)	6.167 ±	0.809	6.786 ±	1.204	5.832 ±	1.348	3.386 ±	0.326 **
Prostate, ventral	(mg)	521.0 ±	124.2	546.9 ±	105.1	517.8 ±	166.9	474.9 ±	94.5
	(mg/g)	0.988 ±	0.194	1.039 ±	0.141	1.000 ±	0.271	0.989 ±	0.205
Submandibular glands	(mg)	686.7 ±	77.3	691.1 ±	94.8	709.5 ±	70.7	599.8 ±	45.8 *
	(mg/g)	1.312 ±	0.086	1.320 ±	0.149	1.391 ±	0.128	1.252 ±	0.140
Seminal vesicles	(mg)	1530.0 ±	247.3	1447.5 ±	198.7	1431.9 ±	243.8	1111.9 ±	157.7 **
	(mg/g)	2.947 ±	0.546	2.767 ±	0.344	2.807 ±	0.435	2.304 ±	0.238 **

Each value shows mean ± S.D.

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

Table 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of males

Group		Control (vehicle: corn oil)		Low dose (<i>p</i> -Cymene 12 mg/kg)		Medium dose (<i>p</i> -Cymene 60 mg/kg)		High dose (<i>p</i> -Cymene 300 mg/kg)	
		10		10		10		10	
Number of males		10		10		10		10	
Body weight	(g)	524.0 ±	57.3	525.1 ±	59.0	512.0 ±	49.0	481.6 ±	35.7
Pituitary gland	(mg)	10.2 ±	2.1	10.3 ±	1.7	9.3 ±	1.1	9.8 ±	1.4
	(mg/g)	0.019 ±	0.003	0.020 ±	0.002	0.018 ±	0.002	0.020 ±	0.003
Thyroid gland	(mg)	25.0 ±	4.8	25.7 ±	5.4	24.9 ±	4.1	23.7 ±	4.5
	(mg/g)	0.048 ±	0.008	0.049 ±	0.009	0.049 ±	0.007	0.050 ±	0.011
Adrenal gland (R)	(mg)	23.5 ±	4.2	24.0 ±	3.6	21.0 ±	3.7	25.1 ±	8.4
	(mg/g)	0.045 ±	0.007	0.046 ±	0.006	0.041 ±	0.005	0.052 ±	0.016
Adrenal gland (L)	(mg)	24.7 ±	5.2	25.0 ±	4.3	23.1 ±	3.8	24.1 ±	3.2
	(mg/g)	0.047 ±	0.009	0.048 ±	0.007	0.045 ±	0.006	0.050 ±	0.008
Adrenal gland	(mg)	48.2 ±	9.2	49.0 ±	7.4	44.1 ±	7.3	49.2 ±	9.4
	(mg/g)	0.092 ±	0.016	0.094 ±	0.013	0.086 ±	0.011	0.102 ±	0.019

Each value shows mean ± S.D.

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

Table 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females

Group		Control (vehicle: corn oil)		Low dose (<i>p</i> -Cymene 12 mg/kg)		Medium dose (<i>p</i> -Cymene 60 mg/kg)		High dose (<i>p</i> -Cymene 300 mg/kg)	
Number of females		10		10		10		9	
Body weight	(g)	285.1 ±	19.9	281.3 ±	18.6	281.3 ±	28.2	246.4 ±	30.7 **
Brain	(mg)	1856.9 ±	80.7	1825.6 ±	47.5	1820.9 ±	100.8	1778.1 ±	56.8
	(mg/g)	6.543 ±	0.577	6.513 ±	0.422	6.507 ±	0.434	7.295 ±	0.707 *
Thymus	(mg)	251.6 ±	71.5	271.5 ±	77.2	246.2 ±	65.1	224.3 ±	53.6
	(mg/g)	0.876 ±	0.210	0.971 ±	0.283	0.891 ±	0.288	0.924 ±	0.253
Heart	(mg)	869.5 ±	58.0	906.8 ±	65.7	871.3 ±	74.0	809.6 ±	103.8
	(mg/g)	3.054 ±	0.170	3.228 ±	0.187	3.113 ±	0.290	3.297 ±	0.318
Lungs	(mg)	1160.0 ±	158.1	1246.9 ±	228.9	1104.9 ±	68.3	1044.4 ±	206.0
	(mg/g)	4.062 ±	0.401	4.448 ±	0.885	3.948 ±	0.289	4.225 ±	0.421
Liver	(mg)	7363.7 ±	386.6	7596.3 ±	657.2	8505.5 ±	946.6 *	9918.0 ±	1688.6 **
	(mg/g)	25.875 ±	1.252	27.014 ±	1.628	30.280 ±	2.168 **	40.240 ±	4.583 **
Kidney (R)	(mg)	970.9 ±	48.5	1008.2 ±	99.2	1014.6 ±	105.9	1060.9 ±	163.6
	(mg/g)	3.413 ±	0.174	3.587 ±	0.291	3.622 ±	0.373	4.307 ±	0.412 **
Kidney (L)	(mg)	965.5 ±	57.0	1007.3 ±	104.5	972.5 ±	100.8	1046.5 ±	163.3
	(mg/g)	3.393 ±	0.196	3.580 ±	0.256	3.471 ±	0.334	4.246 ±	0.396 **
Kidney	(mg)	1936.5 ±	103.0	2015.5 ±	199.5	1987.1 ±	199.8	2107.4 ±	323.4
	(mg/g)	6.806 ±	0.360	7.167 ±	0.529	7.093 ±	0.682	8.554 ±	0.785 **
Spleen	(mg)	546.7 ±	77.9	580.0 ±	86.8	528.9 ±	106.1	480.5 ±	47.9
	(mg/g)	1.914 ±	0.191	2.062 ±	0.263	1.885 ±	0.352	1.963 ±	0.185
Ovary (R)	(mg)	45.7 ±	8.0	44.8 ±	8.0	42.3 ±	9.2	32.1 ±	5.5 **
	(mg/g)	0.161 ±	0.027	0.160 ±	0.032	0.152 ±	0.038	0.131 ±	0.023
Ovary (L)	(mg)	43.8 ±	5.7	41.9 ±	7.1	41.1 ±	8.1	29.1 ±	7.5 **
	(mg/g)	0.154 ±	0.021	0.149 ±	0.024	0.147 ±	0.031	0.118 ±	0.028 *
Ovary	(mg)	89.5 ±	12.2	86.7 ±	12.0	83.4 ±	13.9	61.2 ±	12.5 **
	(mg/g)	0.315 ±	0.043	0.309 ±	0.046	0.299 ±	0.058	0.250 ±	0.048 *
Uterus	(mg)	566.8 ±	204.4	531.7 ±	159.6	594.6 ±	228.2	387.9 ±	135.3
	(mg/g)	1.992 ±	0.727	1.911 ±	0.664	2.083 ±	0.666	1.587 ±	0.577
Submandibular glands	(mg)	452.6 ±	48.4	470.8 ±	52.1	424.1 ±	46.2	391.4 ±	51.3 *
	(mg/g)	1.595 ±	0.213	1.677 ±	0.181	1.512 ±	0.139	1.602 ±	0.217

Each value shows mean ± S.D.

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

Table 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females

Group		Control (vehicle: corn oil)		Low dose (p-Cymene 12 mg/kg)		Medium dose (p-Cymene 60 mg/kg)		High dose (p-Cymene 300 mg/kg)	
Number of females		10		10		10		9	
Body weight	(g)	285.1 ±	19.9	281.3 ±	18.6	281.3 ±	28.2	246.4 ±	30.7 **
Pituitary gland	(mg)	14.3 ±	1.8	13.6 ±	2.1	12.9 ±	1.9	10.3 ±	2.2 **
	(mg/g)	0.050 ±	0.008	0.048 ±	0.006	0.046 ±	0.007	0.042 ±	0.009
Thyroid gland	(mg)	19.0 ±	3.7	17.9 ±	2.1	17.2 ±	3.5	16.3 ±	2.5
	(mg/g)	0.066 ±	0.011	0.064 ±	0.005	0.061 ±	0.012	0.067 ±	0.013
Adrenal gland (R)	(mg)	30.9 ±	6.5	32.0 ±	5.4	28.8 ±	2.6	27.5 ±	5.3
	(mg/g)	0.108 ±	0.022	0.114 ±	0.022	0.103 ±	0.014	0.112 ±	0.021
Adrenal gland (L)	(mg)	32.8 ±	6.0	34.3 ±	6.0	31.1 ±	3.5	29.1 ±	6.3
	(mg/g)	0.115 ±	0.019	0.123 ±	0.023	0.111 ±	0.010	0.118 ±	0.022
Adrenal gland	(mg)	63.7 ±	12.1	66.3 ±	11.1	59.9 ±	5.3	56.6 ±	11.4
	(mg/g)	0.224 ±	0.040	0.237 ±	0.044	0.215 ±	0.023	0.230 ±	0.042

Each value shows mean ± S.D.

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

Table 9
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Macroscopic findings of males

Findings	Group Dose(mg/kg) Grade	Control		p-Cymene		p-Cymene		p-Cymene	
		0		12		60		300	
		-	P	-	P	-	P	-	P
Adipose tissue									
Nodule		9	1	10	0	10	0	10	0
Epididymis									
Nodule		10	0	10	0	10	0	9	1
Small		9	1	10	0	10	0	5	5
Kidney									
Enlargement		10	0	10	0	9	1	7	3
Whitish area		10	0	10	0	10	0	9	1
Liver									
Discoloration, dark colored		10	0	10	0	10	0	9	1
Enlargement		10	0	10	0	10	0	6	4
Nodule		9	1	10	0	10	0	10	0
Whitish area		10	0	10	0	9	1	10	0
Lung									
Discoloration, dark reddish		9	1	10	0	10	0	10	0
Incomplete retention		10	0	9	1	10	0	10	0

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.

Table 9 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Macroscopic findings of males

Findings	Group Dose(mg/kg) Grade	Control		p-Cymene		p-Cymene		p-Cymene	
		0		12		60		300	
		-	P	-	P	-	P	-	P
Spleen									
Recessed area		10	0	10	0	10	0	9	1
Stomach									
Attachment, black substance		10	0	10	0	10	0	9	1
Testis									
Edematous		9	1	10	0	9	1	3	7
Small		9	1	10	0	9	1	0	10

Notes) -: No abnormal changes P : Non-graded change
 Numerals represent the number of animals.

Table 9 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Macroscopic findings of females

Findings	Group Dose(mg/kg) Grade	Control		p-Cymene		p-Cymene		p-Cymene	
		0		12		60		300	
		-	P	-	P	-	P	-	P
Kidney									
Cyst		9	1	10	0	10	0	9	0
Liver									
Diaphragmatic nodule		10	0	10	0	9	1	9	0
Discoloration, dark colored		10	0	10	0	9	1	8	1
Whitish area		10	0	10	0	9	1	9	0
Lung									
Dark reddish spot/area		10	0	9	1	10	0	9	0
Spleen									
Small		10	0	10	0	9	1	8	1
Stomach									
Attachment, black substance		10	0	10	0	10	0	8	1
Reddish area		10	0	10	0	9	1	9	0

Notes) - : No abnormal changes P : Non-graded change
 Numerals represent the number of animals.

Table 10
Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300											
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Brain		10																													
Spinal cord		10																													
Pituitary gland																															
Aberrant craniopharyngeal tissue																				10						0					
Cyst																				9						1					
Hyperplasia, anterior lobe		10 0 0 0 0																		9 1 0 0 0											
Eyeball																															
Mineralization		8 2 0 0 0																		9 1 0 0 0											
Harderian gland																															
Cellular infiltration, lymphocyte		6 3 1 0 0																		9 1 0 0 0											
Porphyrin secretion, increased		9 1 0 0 0																		9 1 0 0 0											
Optic nerve		10																													

Notes) - : 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Nasal cavity																												
Cellular infiltration, inflammatory		10	0	0	0	0																						
Eosinophilic globules		5	5	0	0	0																						
Mineralization		4	5	1	0	0																						
Zymbal gland		10																										
Submandibular gland		10																										
Sublingual gland		10																										
Tongue		10																										
Esophagus		10																										
Trachea		10																										
Aorta		10																										
Thyroid gland																												
Ectopic thymic tissue		9						1																				0
Ultimobranchial body		5						5																				3

Notes) - : 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300														
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE					
Parathyroid gland		10																		9						1								
Thymus																																		
Hyperplasia, epithelial		7	3	0	0	0																	7	3	0	0	0							
Heart																																		
Fibrosis, myocardial		10	0	0	0	0																	9	1	0	0	0							
Necrosis/inflammatory cell infiltrate		4	5	1	0	0																	1	6	3	0	0							
Lung																																		
Accumulation, foam cell		6	4	0	0	0		1	0	0	0	0										5	4	1	0	0								
Cellular infiltration, inflammatory		10	0	0	0	0		1	0	0	0	0										9	1	0	0	0								
Edema		8	1	1	0	0		1	0	0	0	0										9	0	0	1	0								
Hemorrhage		9	1	0	0	0		1	0	0	0	0										9	1	0	0	0								
Metaplasia, osseous		8	2	0	0	0		1	0	0	0	0										8	2	0	0	0								
Mineralization		7	3	0	0	0		1	0	0	0	0										10	0	0	0	0								
Bronchus		10						1												10														

Notes) -: 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																													
Cellular infiltration,																													
	mononuclear cell	8	2	0	0	0		6	4	0	0	0		7	3	0	0	0		8	2	0	0	0					
Deposit, pigment, brown		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		7	3	0	0	0					
Fatty change, hepatocyte		0	1	4	5	0		0	3	3	4	0		2	6	2	0	0		10	0	0	0	0		**	**	**	**
Focus of cellular alteration		10	0	0	0	0		9	1	0	0	0		10	0	0	0	0		9	1	0	0	0					
Hypertrophy, hepatocellular		10	0	0	0	0		10	0	0	0	0		6	3	1	0	0		10	0	0	0	0		#	**	**	**
Necrosis, focal		10	0	0	0	0		7	3	0	0	0		10	0	0	0	0		10	0	0	0	0					
Single cell necrosis,																													
	centrilobular	9	1	0	0	0		9	1	0	0	0		5	5	0	0	0		0	8	2	0	0		**	**	**	**
Tension lipidosis		10					0	7					3	9				1	7										3

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

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Numerals represent the number of animals.

*P<0.05, **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's exact test).

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300												
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE			
Kidney																																
Cellular infiltration, lymphocyte		8	2	0	0	0		8	2	0	0	0		10	0	0	0	0		8	2	0	0	0								
Cellular infiltration, neutrophil		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		7	3	0	0	0								
Congestion		10	0	0	0	0		9	1	0	0	0		9	1	0	0	0		1	7	2	0	0		** , ##						
Dilatation, tubule, diffuse		7	3	0	0	0		7	3	0	0	0		4	5	1	0	0		0	3	6	1	0		** , ##						
Dilatation, tubule, focal		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		9	0	1	0	0								
Hyaline droplet		10	0	0	0	0		10	0	0	0	0		9	1	0	0	0		5	4	1	0	0		#						
Hyperplasia, transitional cell		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		8	2	0	0	0								
Mineralization		6	3	1	0	0		8	2	0	0	0		7	3	0	0	0		6	4	0	0	0								
Necrosis, papillary		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		3	2	5	0	0		** , ##						
Nephropathy, chronic progressive		2	7	1	0	0		1	8	0	1	0		3	5	0	2	0		1	8	1	0	0								
Regeneration, tubule		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		9	1	0	0	0								
Vacuolation, cytoplasmic		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		0	2	7	1	0		** , ##						

Notes) - : 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, **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's exact test).

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control						p-Cymene						p-Cymene									
		0						12						60						300			
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Spleen																							
Deposit, pigment, brown		0	2	8	0	0										0	1	7	2	0			
Fibrosis, focal		10	0	0	0	0										9	1	0	0	0			
Hematopoiesis, extramedullary		0	0	8	2	0										0	0	7	3	0			
Pancreas																							
Cellular infiltration, lymphocyte		9	1	0	0	0										10	0	0	0	0			
Infiltration, fatty		8	2	0	0	0										10	0	0	0	0			
Adrenal gland		10														10							
Stomach																							
Dilatation, gland		10	0	0	0	0										9	1	0	0	0			
Duodenum		10														10							
Jejunum		10														10							
Ileum		10														10							
Cecum		10														10							
Colon		10														10							

Notes) - : 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.

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300											
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Rectum		10																													
Lymph node, submandibular		10																													
Lymph node, mesenteric		10																													
Testis																															
Degeneration/atrophy, tubular		8	1	0	1	0			10	0	0	0	0			8	1	0	0	0	1			**,,##	0	0	0	8	2		
Dilatation, tubular		10	0	0	0	0			9	0	0	1	0			10	0	0	0	0	0			10	0	0	0	0	0		
Edema		9	0	1	0	0			10	0	0	0	0			9	0	0	1	0			**,,##	0	1	5	4	0			
Hyperplasia, Leydig cell		9	1	0	0	0			10	0	0	0	0			9	0	0	1	0			**,,##	0	4	5	1	0			
Epididymis																															
Cell debris		8	1	1	0	0			10	0	0	0	0			9	0	0	1	0			**,,##	0	0	0	6	4			
Cellular infiltration, lymphocyte		9	1	0	0	0			8	2	0	0	0			10	0	0	0	0			10	0	0	0	0	0			
Granuloma, spermatic		10	0	0	0	0			10	0	0	0	0			10	0	0	0	0			9	0	1	0	0				
Reduced sperm		9	0	0	0	1			10	0	0	0	0			9	0	0	1	0			**,,##	0	0	0	8	2			

Notes) - : 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, **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's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300												
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE			
Prostate																																
Atrophy		9	1	0	0	0																				8	2	0	0	0		
Cellular infiltration, lymphocyte		5	4	1	0	0																					7	1	2	0	0	
Seminal vesicle																																
Atrophy		10	0	0	0	0																					8	1	1	0	0	
Coagulating gland		10																									10					
Urinary bladder																																
Cellular infiltration, lymphocyte		9	1	0	0	0																						10	0	0	0	0
Femur		10																										10				
Marrow, femur		10																										10				
Sternum																																
Degeneration, chondromucinous		2	7	1	0	0																						6	4	0	0	0
Marrow, sternum		10																										10				
Skeletal muscle		10																										10				
Sciatic nerve		10																										10				

Notes) - : 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Skin		10																										
Mammary gland		10																										
Adipose tissue																												
Cellular infiltration,																												
mononuclear cell		0	1	0	0	0																						
Fibrosis		0	0	1	0	0																						
Necrosis, fat		0	0	0	1	0																						

Notes) - : 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300											
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Brain		10																													
Spinal cord		10																													
Pituitary gland Cyst		10						0												7						2					
Eyeball Dysplasia, retina		9						1												7						2					
Mineralization		8 2 0 0 0																		9 0 0 0 0											
Harderian gland Cellular infiltration, lymphocyte		6 4 0 0 0																		8 1 0 0 0											
Optic nerve		10																													
Nasal cavity Cellular infiltration, inflammatory		10 0 0 0 0																		8 1 0 0 0											
Eosinophilic globules		4 4 2 0 0																		5 4 0 0 0											
Mineralization		4 5 1 0 0																		2 7 0 0 0											
Zymbal gland		10																													

Notes) -: 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Submandibular gland																												
Cellular infiltration, lymphocyte		9	1	0	0	0																		9	0	0	0	0
Sublingual gland		10																						9				
Tongue		10																						9				
Esophagus		10																						9				
Trachea		10																						9				
Aorta		10																						9				
Thyroid gland																												
Ultimobranchial body		7						3																8				1
Parathyroid gland		10																						8				1
Thymus																												
Hyperplasia, epithelial		8	2	0	0	0																		7	2	0	0	0
Heart																												
Fibrosis, myocardial		9	1	0	0	0																		9	0	0	0	0
Necrosis/inflammatory cell infiltrate		9	1	0	0	0																		9	0	0	0	0

Notes) -: 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.

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300														
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE					
Lung																																		
Accumulation, foam cell		7	3	0	0	0		0	1	0	0	0																6	2	1	0	0		
Edema		9	1	0	0	0		0	0	1	0	0																8	1	0	0	0		
Hemorrhage		10	0	0	0	0		0	1	0	0	0																7	2	0	0	0		
Metaplasia, osseous		9	1	0	0	0		1	0	0	0	0																7	2	0	0	0		
Mineralization		6	4	0	0	0		1	0	0	0	0																7	2	0	0	0		
Bronchus		10						1																				9						

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

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Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+
Liver																											
Cellular infiltration, mononuclear cell		5	5	0	0	0		6	4	0	0	0		5	5	0	0	0		3	6	0	0	0			
Deposit, pigment, brown		10	0	0	0	0		10	0	0	0	0		8	2	0	0	0		7	2	0	0	0			
Fatty change, hepatocyte		2	7	1	0	0		4	4	2	0	0		3	7	0	0	0		3	6	0	0	0			
Focus of cellular alteration		10	0	0	0	0		10	0	0	0	0		9	1	0	0	0		7	2	0	0	0			
Hypertrophy, hepatocellular		10	0	0	0	0		10	0	0	0	0		7	3	0	0	0	**,**	0	1	8	0	0			
Necrosis, focal		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		8	1	0	0	0			
Nodule, hepatodiaphragmatic		10				0		10				0		9				1		9				0			
Single cell necrosis, centrilobular		10	0	0	0	0		10	0	0	0	0		8	2	0	0	0	**,**	1	7	1	0	0			
Tension lipodosis		9				1		8				2		7				3		7				2			

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

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Numerals represent the number of animals.

*P<0.05, **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's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0							p-Cymene 12							p-Cymene 60							p-Cymene 300							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Kidney																														
Cellular infiltration, lymphocyte		9	1	0	0	0				10	0	0	0	0				9	1	0	0	0				9	0	0	0	0
Cellular infiltration, neutrophil		10	0	0	0	0				10	0	0	0	0				10	0	0	0	0				7	2	0	0	0
Congestion		10	0	0	0	0				10	0	0	0	0				10	0	0	0	0				3	6	0	0	0
Cyst		9					1			10				0			10					0			9				0	
Dilatation, tubule, diffuse		8	2	0	0	0				8	2	0	0	0				9	1	0	0	0				2	5	2	0	0
Hyaline droplet		10	0	0	0	0				10	0	0	0	0				8	2	0	0	0				5	4	0	0	0
Hyperplasia, transitional cell		9	1	0	0	0				10	0	0	0	0				10	0	0	0	0				9	0	0	0	0
Mineralization		2	7	1	0	0				2	6	2	0	0				3	7	0	0	0				5	2	2	0	0
Necrosis, papillary		10	0	0	0	0				10	0	0	0	0				10	0	0	0	0				1	6	2	0	0
Nephropathy, chronic progressive		6	4	0	0	0				5	5	0	0	0				6	4	0	0	0				5	4	0	0	0
Regeneration, tubule		10	0	0	0	0				10	0	0	0	0				10	0	0	0	0				6	3	0	0	0
Vacuolation, cytoplasmic		10	0	0	0	0				10	0	0	0	0				10	0	0	0	0				0	4	5	0	0

Notes) - : 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, **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's exact test).

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Spleen																												
	Deposit, pigment, brown	0	0	2	6	2																						
	Hematopoiesis, extramedullary	0	2	8	0	0																						
Pancreas																												
	Cellular infiltration, lymphocyte	9	1	0	0	0																						
	Decrease, zymogen granule	10	0	0	0	0																						
Adrenal gland																												
	Focus of vacuolation	10	0	0	0	0																						
	Hypertrophy, cortical cell	10	0	0	0	0																						
Stomach																												
	Congestion	10	0	0	0	0																						
Duodenum																												
		10																										
Jejunum																												
		10																										
Ileum																												
		10																										
Cecum																												
		10																										

Notes) -: 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+
Colon		10												9													
Rectum		10												9													
Lymph node, submandibular		10												9													
Lymph node, mesenteric		10												9													
Ovary																											
Increased number, atretic follicle		10	0	0	0	0	0							8	0	1	0	0									
Oviduct		10												9													
Uterus																											
Atrophy		10	0	0	0	0	0							8	0	1	0	0									
Vagina																											
Mucinous degeneration		10	0	0	0	0	0							8	1	0	0	0									
Urinary bladder		10												9													
Femur																											
Bone, decreased, trabecula		10	0	0	0	0	0							8	0	1	0	0									
Marrow, femur																											
Hematopoiesis, decreased		10	0	0	0	0	0							8	0	0	1	0									

Notes) - : 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.

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Findings	Group Dose(mg/kg) Grade	Control 0						p-Cymene 12						p-Cymene 60						p-Cymene 300									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Sternum																													
Degeneration, chondromucinous		5	5	0	0	0																			4	5	0	0	0
Marrow, sternum																													
Hematopoiesis, decreased		10	0	0	0	0																			8	0	1	0	0
Skeletal muscle		10																							9				
Sciatic nerve		10																							9				
Skin		10																							9				
Mammary gland		10																							9				

Notes) -: 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.

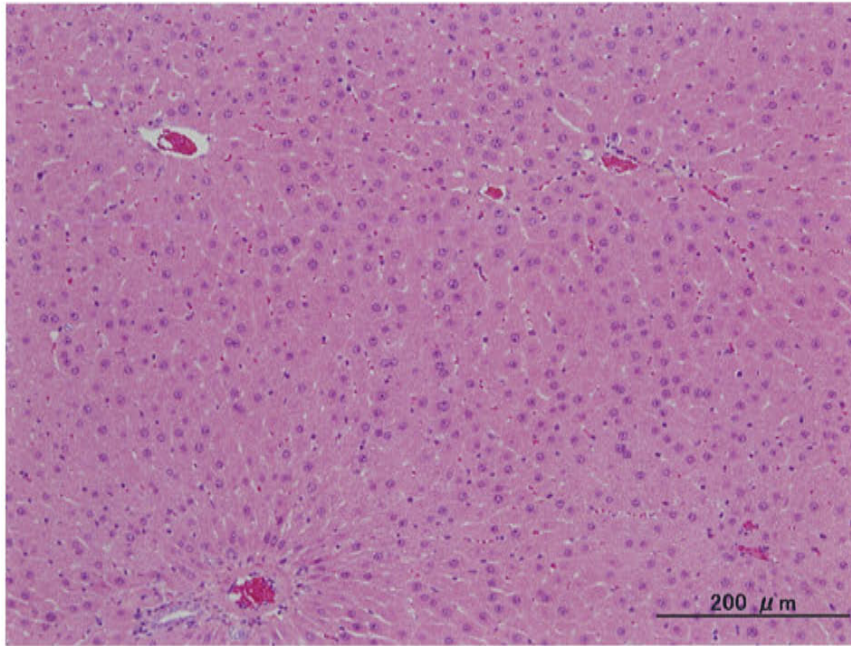


Photo 1

Microphotograph of the liver in the high dose group (Animal No. M04032), HE stain
Hepatocellular hypertrophy with eosinophilic change, and single cell necrosis in hepatocytes
are observed in the centrilobular area.

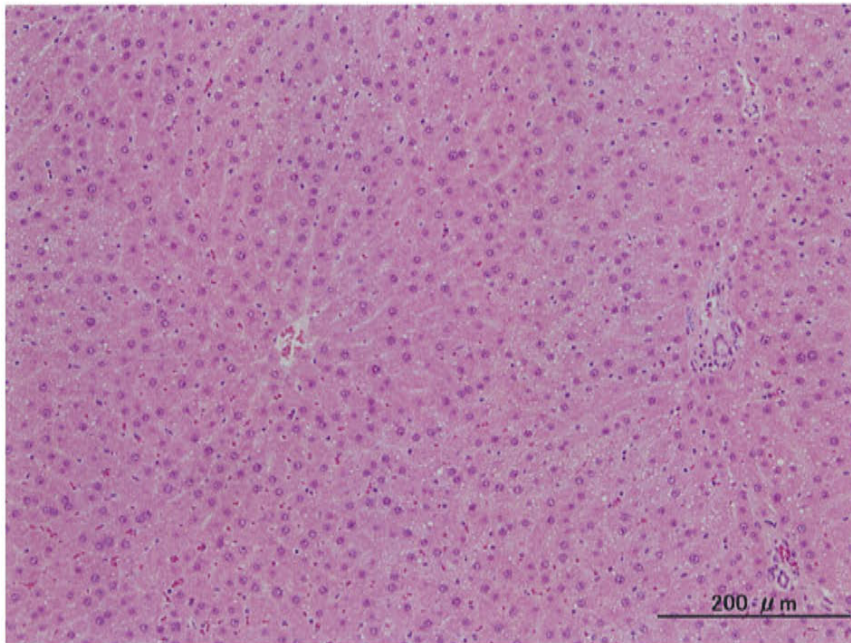


Photo 2

Microphotograph of the liver in the control group (Animal No. M01004), HE stain
Fatty change of hepatocytes are observed in the periportal area.

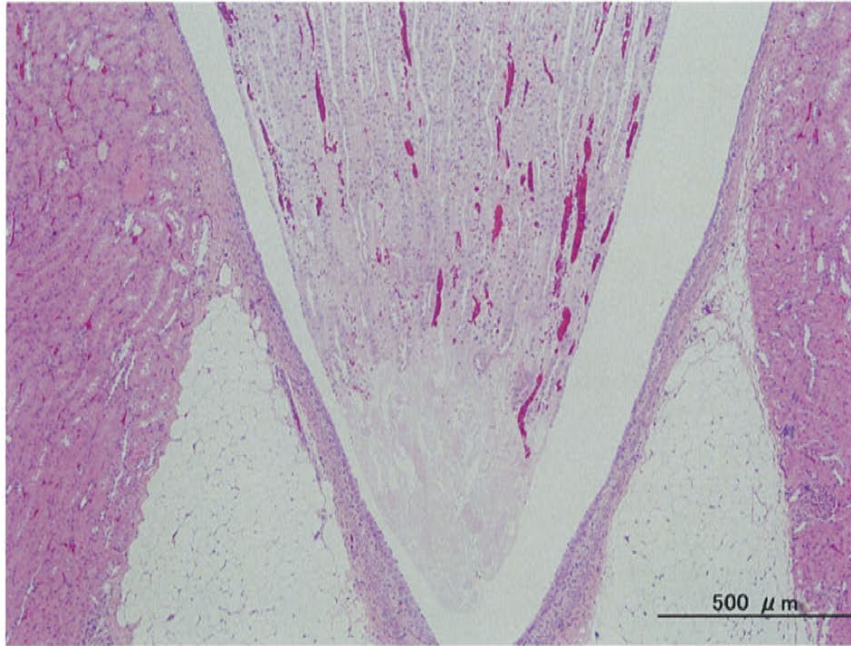


Photo 3

Microphotograph of the kidney in the high dose group (Animal No. M04033), HE stain
Papillary necrosis and congestion are observed in the papillary tip.

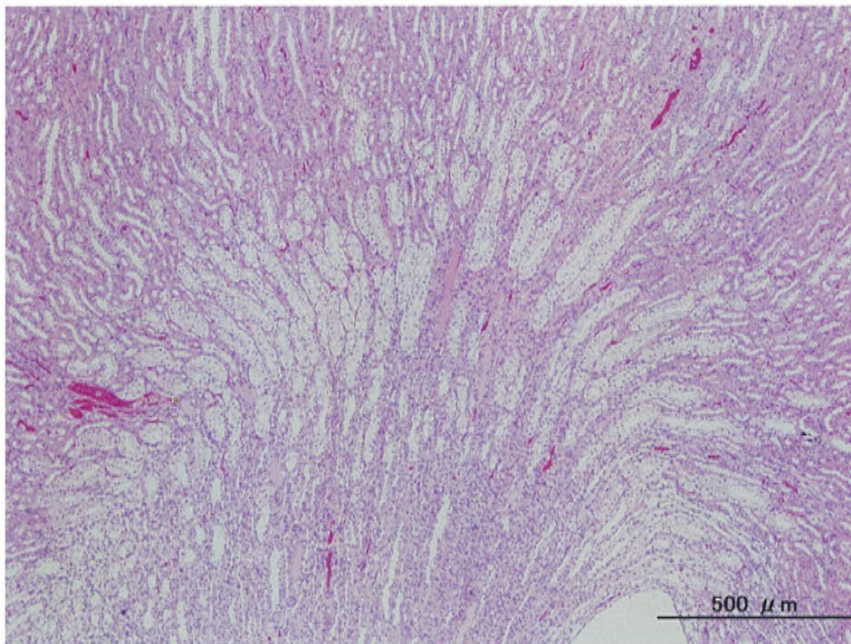


Photo 4

Microphotograph of the kidney in the high dose group (Animal No. M04033), HE stain
Cytoplasmic vacuolation of collecting ducts are observed in outer zone of the inner medulla.

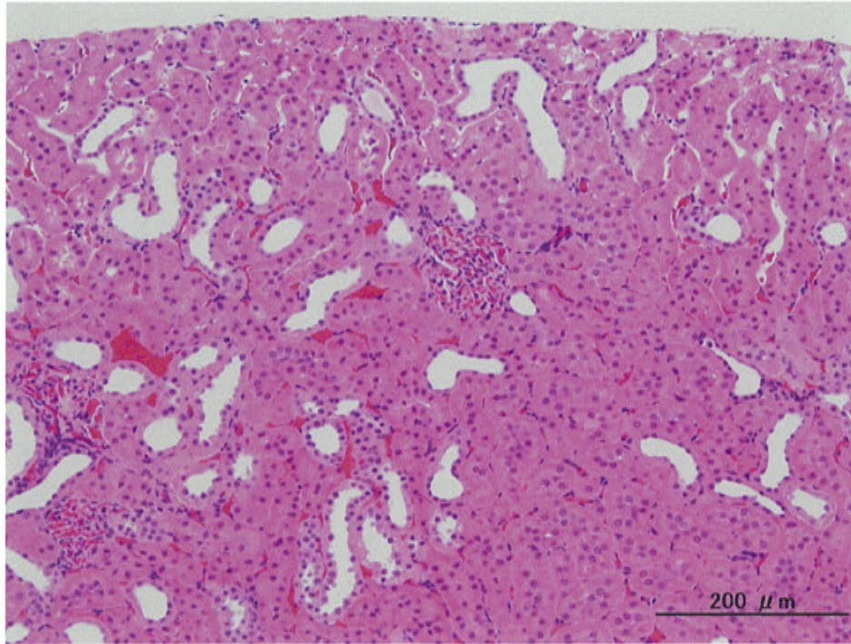


Photo 5

Microphotograph of the kidney in the high dose group (Animal No. M04040), HE stain
Dilatation of distal tubules is observed in the cortex.

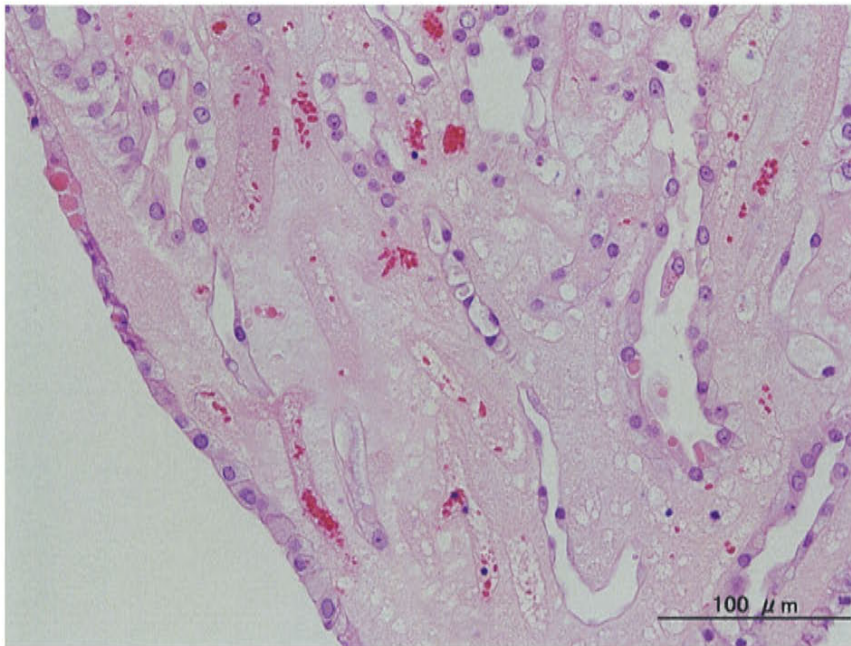


Photo 6

Microphotograph of the kidney in the high dose group (Animal No. M04037), HE stain
Papillary necrosis, and hyaline droplets of papillary epithelium and papillary duct are observed.

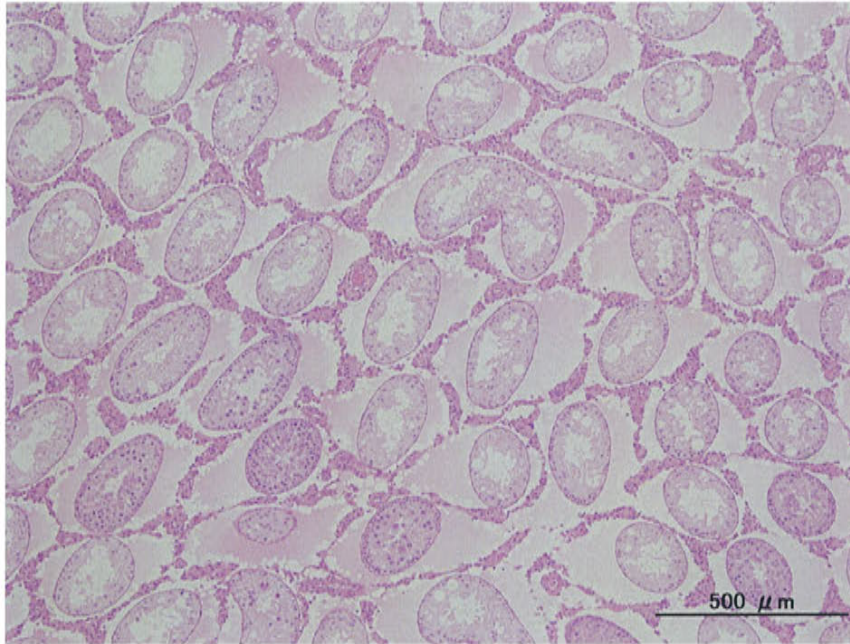


Photo 7

Microphotograph of the testis in the high dose group (Animal No. M04032), HE stain. Degeneration and atrophy of seminiferous tubules, diffuse hyperplasia of Leydig cell, and interstitial edema are observed.



Photo 8

Microphotograph of the epididymis in the high dose group (Animal No. M04032), HE stain. Reduced sperm with cell debris are observed in the lumen.

Appendix 1

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Control (vehicle: corn oil)

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

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
M04031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Control (vehicle: corn oil)

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
M04031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Control (vehicle: corn oil)

Male No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
M04031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Control (vehicle: corn oil)

Male No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
M04031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Control (vehicle: corn oil)

Male No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10
a	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	0

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
M02011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10
a	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	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	10	10	10	10	10
a	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	0

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
M04031	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04032	-	a	-	a	-	-	-	-	a	-	a	-	a	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-
M04033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-
M04034	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
M04035	-	a	-	a	-	a	-	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	-	-	a	-	a	-
M04036	-	-	-	-	-	a	-	-	-	-	a	-	a	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-
M04037	-	-	-	-	-	a	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	a	-	-	-	-	a
M04038	-	a	-	a	-	a	-	a	-	a	-	-	-	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-
M04039	-	-	-	a	-	-	-	-	-	-	a	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	a	-	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	-	-	a	-	a	-	a	-
Number of males	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	5	10	5	10	8	10	6	10	4	10	5	10	7	10	3	10	4	10	8	10	6	10	6	10	5
a	0	5	0	5	0	5	0	2	0	4	0	6	0	5	0	3	0	7	0	6	0	2	0	4	0	4	0	5

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration																																															
	71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91							
	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	Pre	Post	Pre	Post	Pre	Post	Pre							
M03021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
M03022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M03023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
M03024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	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	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	
a	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	0	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	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	0

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration																																														
	71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91						
	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	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre				
M04031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
M04032	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	
M04033	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04034	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04036	-	-	-	a	-	-	-	-	-	-	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04037	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
M04039	-	-	-	-	-	a	-	a	-	a	-	-	-	a	-	a	-	-	-	-	-	-	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-
M04040	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	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	6	10	6	10	5	10	3	10	4	10	5	10	4	10	5	10	6	10	7	10	8	10	7	10	2	10	2	10	7	10	6	9	4	10	5	10	5	10	5	10	5	10	5	10		
a	0	4	0	4	0	5	0	7	0	6	0	5	0	6	0	5	0	4	0	3	0	2	0	3	0	8	0	8	0	3	0	4	0	6	0	5	0	5	0	5	0	5	0	5	0	5	0
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	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.

a: Mouth, Salivation.

b: Excretion, Reddish urine.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Control (vehicle: corn oil)

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
F01041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
F02051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
	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
F04071	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04072	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04073	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04074	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04075	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04080	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Control (vehicle: corn oil)

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
F01041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
F02051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																											
	15		16		17		18		19		20		21		22		23		24		25		26		27		28	
	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
F04071	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04072	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04073	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04074	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04075	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04080	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Control (vehicle: corn oil)

Female No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
F01041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
F02051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																											
	29		30		31		32		33		34		35		36		37		38		39		40		41		42	
	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
F04071	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04072	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04073	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04074	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04075	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04080	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Control (vehicle: corn oil)

Female No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
F01041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0
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	0	0
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	0	0	0	0
d	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	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	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	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	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	0
i	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	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.

c: General appearance, Emaciation.

d: Excretion, Anuria.

e: Posture, Body position, Prone position.

f: Body temperature, Hypothermia.

g: Behavior, Loss of locomotor activity.

h: Breathing, Agonal respiration.

i: Excretion, No-feces.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
F02051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0
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	0	0
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	0	0	0	0
d	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	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	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	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	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	0
i	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	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.

c: General appearance, Emaciation.

d: Excretion, Anuria.

e: Posture, Body position, Prone position.

f: Body temperature, Hypothermia.

g: Behavior, Loss of locomotor activity.

h: Breathing, Agonal respiration.

i: Excretion, No-feces.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0
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	0	0
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	0	0	0	0
d	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	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	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	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	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	0
i	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	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening

c: General appearance, Emaciation.

d: Excretion, Anuria.

e: Posture, Body position, Prone position.

f: Body temperature, Hypothermia.

g: Behavior, Loss of locomotor activity.

h: Breathing, Agonal respiration.

i: Excretion, No-feces.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																											
	43		44		45		46		47		48		49		50		51		52		53		54		55		56	
	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
F04071	-	b	a	a,b	a,c	a,b,c,d,e,f,g,h,i	(sacrificed)																					
F04072	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04073	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04074	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04075	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04080	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
-	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
a	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	1	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	1	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	1	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	1	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	0	0	0	1	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.

a: Excretion, Decrease in amount of feces.

b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.

c: General appearance, Emaciation.

d: Excretion, Anuria.

e: Posture, Body position, Prone position.

f: Body temperature, Hypothermia.

g: Behavior, Loss of locomotor activity.

h: Breathing, Agonal respiration.

i: Excretion, No-feces.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Control (vehicle: corn oil)

Female No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
F01041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
F02051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	10	10	10	10	10
a	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	0

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																											
	57		58		59		60		61		62		63		64		65		66		67		68		69		70	
	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
F04072	-	a	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-
F04073	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
F04074	-	-	-	a	-	-	-	a	-	-	-	a	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-
F04075	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04080	-	-	-	a	-	a	-	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
-	9	7	9	6	9	7	9	7	9	7	9	6	9	6	9	5	9	6	9	6	9	6	9	6	9	6	9	6
a	0	2	0	3	0	2	0	2	0	2	0	3	0	3	0	4	0	3	0	3	0	3	0	3	0	3	0	3

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Mouth, Salivation.

Appendix 1 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

General condition of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration																																																	
	71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91		92							
	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	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
F03061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
F03062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F03063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F03064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03069	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F03070	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
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	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	
a	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	0	0	0	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	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	0	0	0
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	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

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration																																																	
	71		72		73		74		75		76		77		78		79		80		81		82		83		84		85		86		87		88		89		90		91		92							
	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	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
F04072	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F04073	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	
F04074	-	a	-	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	-	a	
F04075	c	c	c	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04076	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04077	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04078	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04079	-	-	-	-	-	-	-	-	a	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F04080	-	a	-	a	-	a	-	a	-	a	-	a	-	a,b	-	a,b	-	a	-	b	-	a	-	a,b	-	a	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
-	8	6	8	7	9	6	9	5	9	5	9	6	9	5	9	5	9	5	9	6	9	6	9	7	9	4	9	4	9	7	9	7	8	7	8	7	8	7	9	6	9	6	9	7	9	9	9			
a	0	2	0	2	0	3	0	4	0	4	0	3	0	4	0	4	0	4	0	3	0	2	0	2	0	5	0	5	0	2	0	2	0	2	0	2	0	3	0	3	0	3	0	2	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	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	0	0	0
c	1	1	1	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	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.
 a: Mouth, Salivation.
 b: Excretion, Reddish urine.
 c: Excretion, Decrease in amount of feces.

Appendix 2

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Body weight of males

Control (vehicle: corn oil)

Male No.	Days of administration													
	1	8	15	22	29	36	43	50	57	64	71	78	85	90
M01001	137.4	197.2	253.9	313.5	367.7	421.6	458.4	492.8	520.4	547.5	559.7	581.4	596.0	603.5
M01002	132.7	193.6	247.0	304.2	358.4	411.5	444.5	469.2	493.2	517.5	539.5	557.8	576.1	580.3
M01003	127.1	187.5	234.2	288.8	338.9	373.2	396.7	418.3	440.8	461.5	464.6	486.7	501.1	504.1
M01004	139.8	205.1	259.9	308.3	346.4	377.8	408.9	426.4	456.0	482.4	492.6	507.3	523.5	525.3
M01005	134.9	201.3	262.3	315.4	360.0	401.6	430.7	470.5	484.7	499.8	524.5	537.5	548.7	542.0
M01006	131.6	178.9	215.2	248.9	279.5	302.4	326.3	345.4	366.2	383.1	397.0	412.3	429.4	437.3
M01007	136.7	186.0	240.5	299.5	348.5	379.1	407.2	435.3	459.4	485.4	510.1	532.4	547.0	555.8
M01008	138.9	205.2	265.1	326.7	386.0	435.9	477.0	509.2	545.3	565.5	589.1	612.0	628.7	642.0
M01009	126.5	183.4	228.8	277.5	318.3	354.3	382.4	405.9	432.6	446.2	464.2	477.0	498.8	509.5
M01010	138.0	203.7	264.4	319.5	362.1	402.7	439.3	468.6	495.2	525.5	540.1	557.5	580.4	591.5
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	134.4	194.2	247.1	300.2	346.6	386.0	417.1	444.2	469.4	491.4	508.1	526.2	543.0	549.1
S.D.	4.8	9.7	17.1	23.2	29.7	38.3	43.1	48.1	50.5	53.1	55.7	57.6	57.4	58.8

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration													
	1	8	15	22	29	36	43	50	57	64	71	78	85	90
M02011	143.4	208.8	265.1	327.3	386.0	434.1	475.0	505.3	537.7	562.6	595.2	615.2	636.9	648.2
M02012	132.7	184.3	230.0	275.4	317.0	351.2	369.1	388.0	404.9	414.5	424.8	434.2	448.0	456.2
M02013	142.2	202.0	258.3	321.4	368.1	413.0	452.1	482.8	510.6	525.5	547.7	567.2	596.1	593.9
M02014	132.2	200.8	261.1	310.7	357.4	402.2	436.3	459.9	485.8	506.3	527.3	546.2	559.1	562.0
M02015	131.9	177.8	220.2	273.4	320.7	350.9	377.3	402.5	418.6	440.1	459.2	477.5	496.5	500.7
M02016	128.3	183.4	237.9	287.4	335.8	371.5	402.1	430.3	454.2	471.2	486.8	507.2	524.9	529.0
M02017	138.6	202.6	259.1	310.3	355.4	382.2	414.9	441.0	463.3	481.9	493.7	508.4	518.9	532.9
M02018	137.6	193.0	247.3	292.0	330.3	366.1	398.8	422.6	446.0	465.2	488.5	509.2	528.5	535.9
M02019	128.3	182.0	226.7	285.1	341.2	390.4	436.1	481.9	525.1	550.8	574.3	597.3	618.7	636.0
M02020	131.2	176.5	224.3	280.0	318.0	361.2	388.8	411.9	439.5	450.5	463.1	487.8	498.1	506.4
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	134.6	191.1	243.0	296.3	343.0	382.3	415.1	442.6	468.6	486.9	506.1	525.0	542.6	550.1
S.D.	5.5	11.7	17.2	19.6	23.2	27.6	34.2	38.7	44.9	48.5	54.0	56.1	59.6	60.7
Significance	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

Unit: g

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

Appendix 2 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Body weight of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration													
	1	8	15	22	29	36	43	50	57	64	71	78	85	90
M03021	128.3	185.2	232.1	286.4	324.9	362.4	392.3	421.8	437.6	456.0	475.2	487.8	501.1	502.9
M03022	123.0	179.0	231.9	273.8	320.1	363.9	395.4	416.2	442.7	459.1	471.8	493.2	508.7	513.9
M03023	137.5	205.0	257.4	309.3	352.5	386.1	421.8	434.4	463.0	476.8	499.4	511.2	537.3	546.4
M03024	131.7	187.9	233.5	280.5	321.6	353.0	376.6	394.0	415.6	424.9	437.1	450.3	458.5	463.0
M03025	141.4	218.3	281.2	345.3	398.4	431.8	462.7	490.3	516.8	533.5	557.3	576.8	597.3	609.0
M03026	125.0	176.7	221.4	261.5	304.7	327.7	355.6	375.3	398.3	410.6	420.1	441.6	458.4	473.0
M03027	131.1	187.4	241.9	306.7	362.4	397.6	440.2	465.3	495.6	513.5	532.0	550.5	559.0	575.8
M03028	134.5	197.6	241.6	291.7	338.1	372.1	403.3	433.9	451.3	478.6	495.0	512.6	527.4	539.5
M03029	139.3	209.0	267.2	329.1	376.7	414.4	460.6	485.5	512.2	538.7	548.8	567.6	581.9	600.3
M03030	132.3	192.0	244.2	302.4	354.8	392.7	423.1	452.9	475.9	499.7	513.7	535.5	554.4	567.3
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	132.4	193.8	245.2	298.7	345.4	380.2	413.2	437.0	460.9	479.1	495.0	512.7	528.4	539.1
S.D.	6.0	13.5	18.3	25.4	29.0	30.7	35.1	37.4	39.6	43.1	45.2	46.0	47.4	50.5
Significance	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

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration													
	1	8	15	22	29	36	43	50	57	64	71	78	85	90
M04031	131.1	188.5	244.6	291.7	330.6	368.9	394.5	427.3	447.9	462.8	484.9	496.2	500.6	512.6
M04032	140.7	204.4	257.6	317.5	367.4	396.7	421.9	442.6	463.6	478.4	488.7	495.4	498.1	504.1
M04033	146.5	217.6	274.3	323.4	366.8	406.7	426.5	452.7	473.0	493.6	503.4	523.5	535.4	530.1
M04034	129.9	186.4	230.6	287.4	330.1	353.2	374.3	386.0	421.3	428.6	440.0	453.1	458.4	450.0
M04035	134.8	202.7	250.9	298.7	340.3	390.4	431.7	460.2	492.6	511.1	534.1	554.8	577.4	580.4
M04036	136.6	191.0	247.4	309.8	359.0	401.1	442.0	464.7	489.2	507.4	523.7	536.7	546.9	555.4
M04037	136.4	194.0	241.5	280.5	317.8	345.9	384.4	405.0	430.7	457.9	471.0	485.6	494.5	504.4
M04038	131.4	180.3	224.7	280.3	330.1	365.5	391.7	409.8	437.9	456.7	474.2	484.3	500.7	495.0
M04039	135.0	206.5	262.4	323.6	366.0	399.3	415.7	440.6	452.0	473.0	493.1	504.8	516.5	524.1
M04040	130.0	186.6	236.6	290.4	338.0	365.2	391.1	409.3	434.3	442.8	457.3	458.8	473.6	487.9
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	135.2	195.8	247.1	300.3	344.6	379.3	407.4	429.8	454.3	471.2	487.0	499.3	510.2	514.4
S.D.	5.2	11.6	15.0	17.0	18.5	22.0	22.9	26.5	24.7	27.0	28.7	32.2	35.2	36.2
Significance	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

Unit: g

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

Appendix 2 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Body weight of females

Control (vehicle: corn oil)

Female No.	Days of administration														
	1	8	15	22	29	36	43	45	50	57	64	71	78	85	91
F01041	139.1	165.2	190.6	216.6	231.9	242.7	258.0		273.5	280.5	281.5	296.9	307.4	311.7	314.5
F01042	130.6	164.0	186.1	208.6	228.5	232.4	250.2		262.5	270.3	272.4	283.1	291.7	290.8	293.4
F01043	126.7	159.4	172.9	204.0	222.1	237.9	242.1		265.9	276.2	283.2	287.2	304.3	311.7	311.6
F01044	133.1	171.6	188.2	218.1	236.5	249.6	271.4		288.2	302.5	309.3	326.2	337.6	343.3	348.3
F01045	124.6	157.8	163.1	187.0	199.4	211.5	223.5		230.8	244.5	260.4	272.9	270.1	273.0	281.7
F01046	126.8	143.6	160.6	180.4	196.8	202.8	216.9		229.4	241.3	239.1	249.7	260.3	268.9	273.1
F01047	135.1	170.8	189.6	201.4	226.9	238.9	252.9		259.4	263.4	277.5	283.2	288.7	285.0	293.7
F01048	125.0	144.5	167.3	186.2	204.9	221.1	232.3		241.4	252.2	261.8	269.5	282.5	284.5	293.3
F01049	126.5	152.8	167.7	196.0	214.7	223.7	232.1		244.9	259.4	270.0	273.3	282.8	297.4	296.7
F01050	129.3	161.1	168.9	189.3	211.3	225.5	236.4		253.3	273.5	279.0	280.5	293.5	306.0	301.3
Number of females	10	10	10	10	10	10	10		10	10	10	10	10	10	10
Mean	129.7	159.1	175.5	198.8	217.3	228.6	241.6		254.9	266.4	273.4	282.3	291.9	297.2	300.8
S.D.	4.8	9.7	11.8	13.1	14.0	14.5	16.7		18.8	18.4	18.2	19.9	21.4	22.0	20.7

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration															
	1	8	15	22	29	36	43	45	50	57	64	71	78	85	91	
F02051	137.2	167.2	170.2	195.6	219.3	260.5	265.3		259.2	275.1	283.5	295.4	291.8	306.9	310.0	
F02052	130.3	166.4	190.2	212.8	225.9	250.8	263.9		277.8	279.2	292.4	307.0	311.8	308.9	319.6	
F02053	129.7	160.2	193.4	209.5	239.6	251.9	262.5		273.0	269.8	290.0	296.3	310.3	313.2	316.1	
F02054	131.4	167.6	179.5	200.7	217.6	230.4	234.8		250.1	264.4	269.0	270.6	285.7	295.1	294.1	
F02055	127.1	161.1	176.2	202.3	223.6	236.5	253.8		266.8	278.6	282.5	299.2	310.5	315.7	316.9	
F02056	137.0	166.4	175.8	186.4	206.1	215.4	227.8		230.4	246.0	253.3	260.5	261.4	276.0	280.6	
F02057	123.7	159.0	168.9	190.8	204.7	218.3	228.2		231.2	254.4	258.3	270.6	277.0	281.4	285.9	
F02058	132.7	152.2	170.3	179.3	195.8	206.5	215.9		228.3	239.5	249.7	260.0	264.7	272.7	275.2	
F02059	125.0	151.4	166.0	185.8	206.5	225.2	232.0		243.8	266.2	269.9	277.1	286.0	298.9	301.0	
F02060	129.5	157.1	168.7	188.3	200.9	215.6	224.6		234.7	234.9	246.5	257.3	257.7	258.3	270.6	
Number of females	10	10	10	10	10	10	10		10	10	10	10	10	10	10	
Mean	130.4	160.9	175.9	195.2	214.0	231.1	240.9		249.5	260.8	269.5	279.4	285.7	292.7	297.0	
S.D.	4.5	6.1	9.3	11.0	13.5	18.3	18.6		18.7	16.2	17.1	18.5	20.6	19.6	18.3	
Significance	NS	NS	NS	NS	NS	NS	NS	---	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	AN	AN	AN	NA	AN	AN	AN	AN	AN	AN	AN	DU

Unit: g

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

NA: Not analyzed.

Appendix 2 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Body weight of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration															
	1	8	15	22	29	36	43	45	50	57	64	71	78	85	91	
F03061	127.6	156.9	177.9	198.8	218.3	225.8	237.7		245.4	261.0	270.2	293.2	315.5	310.4	314.5	
F03062	134.6	183.5	194.3	216.2	222.6	243.6	254.1		266.7	262.7	280.4	290.6	290.2	288.4	292.0	
F03063	123.0	159.2	174.8	202.1	221.1	237.5	242.0		257.4	265.9	272.3	278.7	282.8	291.2	291.1	
F03064	138.2	175.1	197.7	216.9	247.2	268.0	279.3		285.6	303.6	316.3	324.4	328.9	333.4	335.6	
F03065	126.6	155.9	161.8	177.9	194.9	205.4	211.1		221.7	232.2	242.2	248.1	254.6	261.2	263.3	
F03066	130.0	153.1	172.8	194.1	205.7	215.0	232.7		242.2	248.6	248.6	266.5	269.2	271.4	277.2	
F03067	130.2	162.6	181.5	205.0	228.7	234.8	257.3		268.4	275.5	277.6	290.3	292.2	295.9	298.1	
F03068	123.3	145.4	162.4	181.5	193.8	197.4	214.7		229.9	238.0	243.6	255.0	261.9	273.2	269.8	
F03069	133.6	160.4	177.9	193.0	204.2	215.4	229.8		233.5	251.1	257.7	261.1	264.3	277.2	280.3	
F03070	131.3	170.9	191.7	228.8	244.0	273.0	286.7		304.5	313.2	328.7	341.4	349.8	349.6	360.8	
Number of females	10	10	10	10	10	10	10		10	10	10	10	10	10	10	
Mean	129.8	162.3	179.3	201.4	218.1	231.6	244.5		255.5	265.2	273.8	284.9	290.9	295.2	298.3	
S.D.	4.9	11.3	12.4	16.0	18.7	25.1	25.1		26.2	26.3	29.2	30.0	31.5	28.4	30.7	
Significance	NS	NS	NS	NS	NS	NS	NS	---	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	AN	AN	AN	AN	AN	AN	NA	AN	AN	AN	AN	AN	AN	AN	DU

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration															
	1	8	15	22	29	36	43	45	50	57	64	71	78	85	91	
F04071	133.8	159.0	172.0	191.9	210.3	216.9	200.5	170.2	(sacrificed)							
F04072	128.1	162.8	184.0	200.1	209.6	225.2	240.1		257.9	254.1	256.9	263.6	262.6	265.3	260.2	
F04073	134.0	170.2	188.9	208.6	236.8	255.9	279.9		288.5	313.7	319.4	326.3	330.0	333.4	331.0	
F04074	128.4	154.8	169.6	192.2	203.2	215.3	224.1		225.2	237.0	235.5	240.8	237.9	245.1	244.5	
F04075	123.1	142.4	150.2	164.5	181.2	202.4	206.8		222.2	236.9	242.1	229.5	243.5	246.6	235.6	
F04076	131.4	163.4	178.7	202.6	223.4	235.4	245.4		258.8	269.9	271.7	278.7	283.4	284.4	284.1	
F04077	132.5	170.1	192.9	209.9	228.2	245.3	260.0		256.7	267.2	281.3	285.7	279.6	294.8	290.3	
F04078	120.2	142.7	151.7	163.9	174.5	183.4	197.6		199.0	215.9	222.7	223.0	221.8	219.1	223.5	
F04079	128.0	157.3	166.1	190.8	203.3	214.9	230.9		233.3	241.5	247.7	255.1	258.0	257.0	257.0	
F04080	128.9	155.9	155.3	187.9	213.0	236.5	252.5		256.5	269.4	275.3	276.3	280.8	282.5	279.4	
Number of females	10	10	10	10	10	10	10		9	9	9	9	9	9	9	
Mean	128.8	157.9	170.9	191.2	208.4	223.1	233.8		244.2	256.2	261.4	264.3	266.4	269.8	267.3	
S.D.	4.5	9.7	15.3	16.1	19.4	21.3	27.1		26.6	28.2	29.2	32.0	31.9	33.4	32.8	
Significance	NS	NS	NS	NS	NS	NS	NS	---	NS	NS	NS	NS	NS	NS	*	
Statistical method	AN	AN	AN	AN	AN	AN	AN	NA	AN	AN	AN	AN	AN	AN	AN	DU

Unit: g

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.

NA: Not analyzed.

Appendix 3

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Food consumption of males

Control (vehicle: corn oil)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M01001	19.7	22.1	23.0	26.3	26.9	25.0	27.1	24.5	26.9	22.8	24.9	25.2	25.2
M01002	18.1	18.8	23.3	25.8	26.8	24.3	26.6	23.7	26.4	25.7	26.8	27.4	26.6
M01003	18.5	18.7	20.4	19.3	22.6	20.8	21.1	17.4	21.0	18.2	21.4	23.0	21.0
M01004	20.5	23.8	22.1	24.7	23.0	20.1	20.4	22.3	21.9	19.8	22.4	23.2	21.5
M01005	19.2	22.8	24.9	25.3	23.2	21.5	27.0	21.3	28.0	23.3	20.9	25.3	18.8
M01006	18.7	20.1	20.3	17.4	19.9	18.3	17.9	19.0	21.4	19.5	20.2	15.4	19.9
M01007	18.3	21.4	24.4	23.5	23.0	22.4	22.8	22.5	24.1	24.3	21.3	23.0	23.2
M01008	21.9	25.3	27.1	26.4	30.7	28.9	29.8	28.8	27.4	26.1	28.0	25.5	26.8
M01009	17.8	23.7	23.2	22.4	24.0	22.2	23.3	22.9	23.4	20.0	20.0	21.7	20.2
M01010	20.4	23.2	23.3	21.0	23.9	23.1	24.3	23.6	26.4	24.1	22.3	24.8	26.3
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	19.3	22.0	23.2	23.2	24.4	22.7	24.0	22.6	24.7	22.4	22.8	23.5	23.0
S.D.	1.3	2.2	2.0	3.1	3.0	2.9	3.6	3.1	2.7	2.8	2.8	3.3	3.1

Low dose (*p*-Cymene 12 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M02011	22.1	23.4	25.0	25.6	26.9	26.4	26.2	32.7	30.7	26.0	27.2	30.0	23.6
M02012	19.5	19.4	20.4	19.2	22.2	17.3	19.3	20.6	18.8	15.4	17.2	17.6	15.8
M02013	20.1	23.1	25.0	24.2	26.0	26.6	26.0	24.9	23.5	26.0	23.0	27.3	24.3
M02014	18.9	22.0	23.6	25.4	25.2	21.7	21.4	24.7	25.5	25.0	22.8	22.0	21.6
M02015	18.2	18.8	21.6	24.1	23.4	22.7	20.2	21.9	20.8	19.2	22.3	25.3	20.8
M02016	17.7	22.2	20.6	24.6	25.6	23.7	25.3	23.9	23.8	23.0	23.8	22.5	23.1
M02017	20.9	22.4	23.4	24.5	23.9	21.1	22.8	22.8	24.8	20.8	20.4	21.9	17.9
M02018	19.8	23.0	23.7	22.4	23.9	23.4	21.2	22.8	21.6	23.2	23.8	24.5	21.3
M02019	19.0	21.8	22.9	22.8	26.1	27.2	28.3	30.4	27.6	31.0	27.1	30.7	28.2
M02020	20.4	20.3	24.0	25.0	25.5	24.5	24.9	22.0	22.1	23.1	24.4	22.3	25.8
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	19.7	21.6	23.0	23.8	24.9	23.5	23.6	24.7	23.9	23.3	23.2	24.4	22.2
S.D.	1.3	1.6	1.6	1.9	1.5	3.0	3.0	3.9	3.5	4.2	2.9	4.0	3.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN

Unit: g

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Food consumption of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M03021	19.2	20.7	21.3	22.5	22.8	21.5	23.0	22.3	24.9	23.9	22.0	22.1	20.2
M03022	19.7	21.9	23.3	25.1	24.9	24.1	25.0	26.0	25.1	23.3	23.6	23.0	21.4
M03023	19.6	20.4	24.3	23.7	24.9	24.1	23.1	22.3	22.3	22.4	20.2	21.7	19.8
M03024	19.8	20.9	21.3	21.5	22.0	19.2	22.2	20.7	21.6	20.6	17.5	19.6	19.5
M03025	21.6	25.3	29.2	27.3	30.4	27.0	28.2	26.8	26.8	29.4	26.5	26.0	27.6
M03026	18.6	19.3	21.4	24.6	21.6	21.7	20.4	20.4	21.5	19.7	19.1	20.8	22.1
M03027	18.4	19.4	25.2	24.8	26.1	27.9	22.9	25.9	25.0	22.8	23.6	23.6	22.8
M03028	20.4	23.0	23.5	22.4	22.9	25.2	25.2	26.2	23.8	24.2	23.6	24.9	20.7
M03029	20.5	26.6	25.8	26.5	27.7	27.1	28.0	28.1	27.6	28.5	25.2	27.8	26.4
M03030	20.1	22.4	22.8	27.0	27.4	27.1	27.1	25.5	22.3	19.9	23.9	24.4	23.8
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	19.8	22.0	23.8	24.5	25.1	24.5	24.5	24.4	24.1	23.5	22.5	23.4	22.4
S.D.	0.9	2.4	2.5	2.0	2.9	2.9	2.6	2.7	2.1	3.3	2.8	2.5	2.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN

High dose (*p*-Cymene 300 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M04031	20.4	23.6	23.1	24.6	27.1	26.9	24.1	24.7	26.6	23.2	25.6	25.0	23.4
M04032	19.8	23.8	26.0	28.2	29.4	28.3	28.9	27.6	26.9	19.6	23.6	25.4	25.1
M04033	16.1	21.7	26.6	26.6	25.9	22.4	24.5	22.4	24.3	22.6	25.1	21.8	27.9
M04034	19.5	19.4	24.1	27.7	27.5	25.7	25.0	24.4	23.7	21.6	29.0	21.5	22.2
M04035	18.1	22.5	22.9	27.2	29.2	30.9	26.4	28.0	28.3	27.4	25.0	28.1	28.5
M04036	19.3	21.7	25.3	24.4	27.0	26.3	25.5	27.5	25.8	22.2	22.2	24.6	23.3
M04037	17.8	20.2	20.8	23.4	23.0	23.4	23.3	25.2	24.6	21.6	21.9	22.8	21.3
M04038	17.6	18.7	22.2	24.9	29.1	26.1	25.9	28.0	27.1	27.5	26.5	19.1	21.3
M04039	19.2	23.7	25.5	25.9	29.1	27.5	25.0	26.1	26.2	23.7	25.6	22.0	26.6
M04040	16.8	21.3	22.2	26.1	26.8	24.9	22.3	26.2	24.1	23.1	24.5	22.2	24.4
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	18.5	21.7	23.9	25.9	27.4	26.2	25.1	26.0	25.8	23.3	24.9	23.3	24.4
S.D.	1.4	1.8	1.9	1.6	2.0	2.4	1.8	1.8	1.5	2.5	2.1	2.5	2.6
Significance	NS	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN

Unit: g

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.

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Food consumption of females

Control (vehicle: corn oil)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F01041	20.2	17.7	14.1	17.8	22.0	19.9	14.2	20.3	20.2	19.0	15.3	19.7	21.2
F01042	19.6	18.7	15.1	19.1	16.2	19.0	12.4	17.2	18.2	17.0	13.7	18.0	17.1
F01043	18.3	18.6	16.9	15.5	17.8	18.6	17.7	15.1	18.9	19.7	16.3	15.8	18.2
F01044	19.2	18.7	14.8	17.2	22.3	18.2	15.0	19.8	21.6	16.6	16.5	19.2	20.4
F01045	18.3	16.4	16.3	15.1	11.9	18.3	15.5	17.1	17.9	14.1	18.0	18.5	17.0
F01046	18.9	16.4	12.4	14.8	17.2	17.5	13.5	18.8	18.4	18.7	13.3	19.4	19.9
F01047	17.0	19.2	13.6	16.1	17.5	13.2	17.0	16.7	15.8	14.9	15.7	12.7	14.4
F01048	19.5	17.8	16.0	17.7	14.6	18.7	13.6	18.2	12.1	18.3	13.7	18.0	18.1
F01049	17.5	16.6	17.9	16.3	19.5	18.0	17.5	16.1	20.7	22.5	19.0	16.7	20.9
F01050	18.1	15.4	15.5	11.6	16.4	18.6	17.8	12.7	17.4	17.1	16.1	15.8	16.7
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	18.7	17.6	15.3	16.1	17.5	18.0	15.4	17.2	18.1	17.8	15.8	17.4	18.4
S.D.	1.0	1.3	1.6	2.1	3.2	1.8	2.0	2.3	2.7	2.4	1.9	2.2	2.2

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F02051	18.7	16.4	15.1	12.9	20.0	23.6	17.9	16.4	12.7	17.7	19.6	19.2	13.8
F02052	18.6	19.1	15.7	19.1	20.5	15.7	19.8	23.7	21.6	15.7	21.6	25.1	18.2
F02053	19.9	22.4	20.5	21.1	21.7	11.5	21.2	16.1	21.0	21.0	16.7	22.0	17.4
F02054	18.7	17.1	16.5	12.7	18.2	18.4	16.3	12.0	15.0	15.8	14.6	16.2	15.9
F02055	18.3	16.9	13.0	16.6	19.4	17.9	12.5	17.2	19.4	17.8	12.8	18.1	17.5
F02056	18.2	12.9	16.3	15.0	12.7	17.1	16.8	15.0	12.2	16.7	17.8	17.2	13.3
F02057	16.4	16.1	16.2	17.8	12.2	17.3	15.3	18.3	20.3	15.1	17.2	17.4	18.5
F02058	16.8	18.5	16.5	14.5	17.0	17.3	15.3	12.9	17.2	19.2	17.9	16.9	16.4
F02059	16.6	16.4	17.2	16.6	14.6	16.5	19.6	16.9	10.9	18.7	19.5	19.2	14.7
F02060	19.4	18.5	17.3	11.2	17.0	14.1	19.0	17.9	19.3	12.1	17.9	21.9	16.3
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	18.2	17.4	16.4	15.8	17.3	16.9	17.4	16.6	17.0	17.0	17.6	19.3	16.2
S.D.	1.2	2.5	1.9	3.1	3.3	3.1	2.6	3.2	4.0	2.5	2.5	2.8	1.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	KW	AN	AN	KW	KW	AN	AN	AN	AN	DU	AN

Unit: g

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Food consumption of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F03061	17.5	18.5	18.0	15.8	18.3	12.9	17.8	12.7	20.5	20.2	21.4	20.2	16.8
F03062	19.7	14.8	16.6	17.5	20.1	13.7	17.8	18.1	19.7	11.2	17.2	16.0	17.2
F03063	16.9	17.6	19.0	15.4	15.9	16.6	18.0	15.6	18.4	17.1	16.1	12.1	16.7
F03064	17.6	22.4	20.9	18.8	20.1	19.7	18.7	19.7	18.9	20.7	19.3	16.4	15.3
F03065	16.1	13.7	16.1	11.2	16.7	16.5	16.1	12.7	17.2	17.6	17.4	13.2	18.2
F03066	18.6	15.8	13.9	19.0	18.7	17.9	13.5	18.4	18.8	16.0	14.5	15.2	18.5
F03067	14.6	18.4	13.2	15.9	16.0	17.3	12.9	16.9	16.7	13.9	12.5	12.6	11.9
F03068	18.2	17.7	13.2	14.6	15.7	16.6	13.6	15.4	17.9	18.1	14.9	16.8	16.8
F03069	18.8	16.7	13.4	13.9	18.5	16.6	16.3	16.9	13.5	15.9	17.2	13.3	15.2
F03070	19.0	19.9	20.1	18.3	21.6	19.9	23.2	21.6	21.7	18.7	22.2	19.6	18.4
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	17.7	17.6	16.4	16.0	18.2	16.8	16.8	16.8	18.3	16.9	17.3	15.5	16.5
S.D.	1.5	2.5	3.0	2.5	2.0	2.2	3.1	2.8	2.3	2.9	3.0	2.8	2.0
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	KW	AN	AN	KW	KW	AN	AN	AN	AN	DU	AN

High dose (*p*-Cymene 300 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F04071	16.3	16.6	13.8	15.3	18.9	21.7	0.4 (sacrificed)						
F04072	16.0	16.5	17.5	14.0	19.4	19.4	20.5	16.2	20.3	15.0	18.2	16.4	16.3
F04073	17.6	17.7	17.3	18.8	17.2	24.3	25.4	19.9	22.4	23.2	25.6	26.1	20.4
F04074	17.0	16.9	17.2	15.0	21.2	17.1	15.9	17.0	18.9	17.3	15.6	22.0	17.7
F04075	13.6	13.6	14.2	16.9	13.3	6.7	7.2	10.9	8.7	11.6	10.5	14.3	8.7
F04076	13.5	19.3	17.0	15.3	20.4	18.4	17.3	17.0	17.4	15.8	13.8	15.3	18.0
F04077	18.6	18.9	22.6	19.3	19.2	22.0	20.2	23.0	17.4	20.8	21.7	22.0	16.6
F04078	15.4	17.7	17.3	13.9	16.7	18.4	18.1	15.9	13.8	20.8	15.5	19.6	17.9
F04079	15.7	15.1	13.3	16.3	13.2	16.8	16.0	14.1	19.5	15.6	17.2	17.4	17.3
F04080	15.7	17.7	1.1	17.8	19.5	20.0	20.2	17.1	19.7	17.9	19.3	22.3	16.0
Number of females	10	10	10	10	10	10	10	9	9	9	9	9	9
Mean	15.9	17.0	15.1	16.3	17.9	18.5	16.1	16.8	17.6	17.6	17.5	19.5	16.5
S.D.	1.6	1.7	5.6	1.9	2.8	4.8	7.2	3.4	4.1	3.6	4.4	3.9	3.2
Significance	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	KW	AN	AN	KW	KW	AN	AN	AN	AN	DU	AN

Unit: g

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.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 4
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Ophthalmologic examination of males

Findings	Group	Control (vehicle: corn oil)					Low dose (p-Cymene 12 mg/kg)					Medium dose (p-Cymene 60 mg/kg)					High dose (p-Cymene 300 mg/kg)				
	Male	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04
	No.	001	002	003	004	005	011	012	013	014	015	021	022	023	024	025	031	032	033	034	035
Cornea																					
Band-shaped opacity		RL	-	RL	-	-	RL	-	RL	-	RL	-	-	RL	RL	RL	-	RL	RL	RL	RL
Lens																					
Opacity, nucleus		-	-	-	-	-	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-
Opacity, anterior pole, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	RL	-	-

-, not observed
 R, observed on the right eye
 L, observed on the left eye
 RL, observed on the both eyes

Appendix 4 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Ophthalmologic examination of females

Findings	Group	Control (vehicle: corn oil)					Low dose (p-Cymene 12 mg/kg)					Medium dose (p-Cymene 60 mg/kg)					High dose (p-Cymene 300 mg/kg)				
	Female	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04
	No.	041	042	043	044	045	051	052	053	054	055	061	062	063	064	065	072	073	074	075	076
Cornea																					
Band-shaped opacity	-	RL	-	RL	-	RL	-	RL	-	-	-	RL	RL	-	-	RL	RL	-	RL	-	
Lens																					
Opacity, anterior pole, focal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	L	RL	-	RL	-	
Fundus																					
Retinal folds	RL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Hyper-reflective fundus	-	-	-	-	-	-	-	RL	-	-	-	-	-	-	-	-	-	-	-	-	

-, not observed
 R, observed on the right eye
 L, observed on the left eye
 RL, observed on the both eyes

Appendix 5

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Urinalysis of males

Control (vehicle: corn oil)														
Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	9.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M01002	7.0	2+	-	+	-	-	2+	yellow	-	-	-	-	±	-
M01003	7.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01004	7.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M01005	7.5	2+	-	+	-	±	+	light yellow	-	-	-	-	±	-

Low dose (p-Cymene 12 mg/kg)														
Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02011	8.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02012	8.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M02013	7.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02014	8.0	+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02015	7.5	2+	-	+	-	-	2+	light yellow	-	-	-	-	±	-

Medium dose (p-Cymene 60 mg/kg)														
Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03021	7.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03022	8.0	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03023	8.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M03024	8.5	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M03025	7.0	+	-	+	-	-	+	light yellow	-	-	-	-	±	-

High dose (p-Cymene 300 mg/kg)														
Male No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04031	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04032	8.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04033	8.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04034	7.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M04035	7.5	2+	-	+	-	2+	±	light yellow	+	3+	-	-	±	-

Protein,	-: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤
Glucose,	-: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤
Ketone,	-: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤
Bilirubin,	-: negative; ±: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤
Occult blood,	-: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤
Urobilinogen,	±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤
Turbidity,	-: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
Red Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
White Blood cells,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
Casts,	-: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
Crystals,	-: not observed; ±: a few; +: abundant
Epithelial cells,	-: not observed; ±: a few; +: abundant

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of p-Cymene in rats

Urinalysis of males

Control (vehicle: corn oil)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M01001	14.4	1.052	89.8	235.96	128.7	1.29	3.40	1.85
M01002	7.9	1.068	71.2	236.29	78.8	0.56	1.87	0.62
M01003	16.4	1.043	70.8	189.21	100.1	1.16	3.10	1.64
M01004	10.6	1.069	164.0	319.94 #	165.4	1.74	3.39	1.75
M01005	10.8	1.060	118.4	212.28	113.7	1.28	2.29	1.23
Number of males	5	5	5	5	5	5	5	5
Mean	12.0	1.058	102.8	238.74	117.3	1.21	2.81	1.42
S.D.	3.4	0.011	39.3	49.40	32.5	0.42	0.69	0.50

Low dose (p-Cymene 12 mg/kg)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M02011	13.3	1.063	128.2	281.33	169.7	1.71	3.74	2.26
M02012	12.0	1.051	72.5	199.58	115.2	0.87	2.39	1.38
M02013	13.1	1.067	157.0	289.56	174.6	2.06	3.79	2.29
M02014	17.1	1.048	124.4	240.25	159.9	2.13	4.11	2.73
M02015	16.4	1.047	103.6	228.52	128.2	1.70	3.75	2.10
Number of males	5	5	5	5	5	5	5	5
Mean	14.4	1.055	117.1	247.85	149.5	1.69	3.56	2.15
S.D.	2.2	0.009	31.4	37.49	26.3	0.50	0.67	0.49
Significance	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

#, The re-measurement was carried out after diluting the specimen with distilled water because the first measured value exceeded the higher limit of quantitation range.

The re-measured value was employed as the measured value for the specimen.

S.G.: Specific gravity

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.

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Urinalysis of males

Medium dose (*p*-Cymene 60 mg/kg)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M03021	18.7	1.043	90.8	185.73	106.1	1.70	3.47	1.98
M03022	20.3	1.041	95.4	181.37	112.6	1.94	3.68	2.29
M03023	20.7	1.037	62.8	154.64	79.3	1.30	3.20	1.64
M03024	13.3	1.051	98.7	226.73	120.7	1.31	3.02	1.61
M03025	19.3	1.052	84.5	219.40	119.1	1.63	4.23	2.30
Number of males	5	5	5	5	5	5	5	5
Mean	18.5	1.045	86.4	193.57	107.6	1.58	3.52	1.96
S.D.	3.0	0.006	14.2	29.55	16.8	0.27	0.47	0.34
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

High dose (*p*-Cymene 300 mg/kg)

Male No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
M04031	41.0	1.024	54.0	97.31	55.0	2.21	3.99	2.26
M04032	51.4	1.020	46.3	86.35	50.9	2.38	4.44	2.62
M04033	44.5	1.027	58.6	109.35	65.3	2.61	4.87	2.91
M04034	44.3	1.024	62.2	100.34	68.7	2.76	4.45	3.04
M04035	30.3	1.042	91.1	172.63	105.8	2.76	5.23	3.21
Number of males	5	5	5	5	5	5	5	5
Mean	42.3	1.027	62.4	113.20	69.1	2.54	4.60	2.81
S.D.	7.7	0.009	17.1	34.23	21.7	0.24	0.47	0.37
Significance	**	**	NS	**	*	**	**	**
Statistical method	DU	DU	DU	DU	DU	DU	DU	DU

S.G.: Specific gravity

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.

Appendix 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of females

Control (vehicle: corn oil)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F01041	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F01042	≥ 9.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F01043	6.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F01044	7.0	±	-	±	-	-	+	light yellow	-	-	-	-	±	-
F01045	7.0	+	-	+	-	-	2+	light yellow	-	-	-	-	±	-

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F02051	6.5	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
F02052	7.0	2+	-	+	+	-	2+	yellow	-	-	-	-	±	-
F02053	6.5	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F02054	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
F02055	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F03061	7.5	±	-	±	-	-	±	light yellow	-	-	-	-	±	-
F03062	6.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F03063	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
F03064	6.0	+	-	+	-	-	±	light yellow	-	-	-	-	-	-
F03065	6.5	±	-	±	-	-	±	light yellow	-	-	-	-	-	-

High dose (*p*-Cymene 300 mg/kg)

female No.	Quality									Urinary sediments				
	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Color	Turbidity	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F04072	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F04073	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F04074	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
F04075	8.0	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F04076	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-

Protein, -: negative; ±: 10 ≤ and < 30 mg/dL; +: 30 ≤ and < 100 mg/dL; 2+: 100 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 600 mg/dL; 4+: 600 mg/dL ≤
 Glucose, -: negative; ±: 30 ≤ and < 70 mg/dL; +: 70 ≤ and < 150 mg/dL; 2+: 150 ≤ and < 300 mg/dL; 3+: 300 ≤ and < 1,000 mg/dL; 4+: 1,000 mg/dL ≤
 Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL; 3+: 80 ≤ and < 150 mg/dL; 4+: 150 mg/dL ≤
 Bilirubin, -: negative; +: 0.5 ≤ and < 2.0 mg/dL; 2+: 2.0 ≤ and < 6.0 mg/dL; 3+: 6.0 ≤ and < 10.0 mg/dL; 4+: 10.0 mg/dL ≤
 Occult blood, -: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL; 3+: 1.00 mg/dL ≤
 Urobilinogen, ±: normal; +: 2.0 ≤ and < 4.0 mg/dL; 2+: 4.0 ≤ and < 8.0 mg/dL; 3+: 8.0 ≤ and < 12.0 mg/dL; 4+: 12.0 mg/dL ≤
 Turbidity, -: negative; ±: trace; +: slight; 2+: moderate; 3+: marked
 Red Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
 White Blood cells, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
 Casts, -: not observed; ±: 1-9/3 visual field; +: 10-99/3 visual field; 2+: 100-299/3 visual field; 3+: ≥ 300/3 visual field
 Crystals, -: not observed; ±: a few; +: abundant
 Epithelial cells, -: not observed; ±: a few; +: abundant

Appendix 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of females

Control (vehicle: corn oil)

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F01041	13.6	1.047	110.7	224.27	130.2	1.51	3.05	1.77
F01042	9.4	1.062	127.7	267.75	160.4	1.20	2.52	1.51
F01043	9.0	1.060	130.4	255.20	150.8	1.17	2.30	1.36
F01044	16.1	1.043	113.3	210.44	136.2	1.82	3.39	2.19
F01045	10.0	1.053	123.1	268.21	173.0	1.23	2.68	1.73
Number of females	5	5	5	5	5	5	5	5
Mean	11.6	1.053	121.0	245.17	150.1	1.39	2.79	1.71
S.D.	3.1	0.008	8.7	26.38	17.5	0.28	0.43	0.31

Low dose (*p*-Cymene 12 mg/kg)

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na mEq/L	K mEq/L	Cl mEq/L	Na mEq/24hr	K mEq/24hr	Cl mEq/24hr
F02051	7.1	1.076	150.4	343.94 #	213.4	1.07	2.44	1.52
F02052	8.0	1.070	141.1	326.76 #	184.9	1.13	2.61	1.48
F02053	15.7	1.035	68.9	149.14	92.0	1.08	2.34	1.44
F02054	12.0	1.051	114.5	230.07	143.6	1.37	2.76	1.72
F02055	12.9	1.048	106.7	226.40	132.7	1.38	2.92	1.71
Number of females	5	5	5	5	5	5	5	5
Mean	11.1	1.056	116.3	255.26	153.3	1.21	2.61	1.57
S.D.	3.6	0.017	32.1	80.16	47.1	0.16	0.23	0.13
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DU	DU	DU	DU	AN	KW	KW

#, The re-measurement was carried out after diluting the specimen with distilled water because the first measured value exceeded the higher limit of quantitation range.

The re-measured value was employed as the measured value for the specimen.

S.G.: Specific gravity

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 5 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Urinalysis of females

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
			mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F03061	19.0	1.037	91.0	171.11	110.3	1.73	3.25	2.10
F03062	12.3	1.032	61.7	78.22	36.6	0.76	0.96	0.45
F03063	17.0	1.042	87.6	201.96	109.9	1.49	3.43	1.87
F03064	14.8	1.026	38.6	57.92	19.4	0.57	0.86	0.29
F03065	20.4	1.032	78.5	144.75	81.0	1.60	2.95	1.65
Number of females	5	5	5	5	5	5	5	5
Mean	16.7	1.034	71.5	130.79	71.4	1.23	2.29	1.27
S.D.	3.2	0.006	21.6	61.15	41.8	0.53	1.27	0.84
Significance	NS	*	*	*	*	NS	NS	NS
Statistical method	DT	DU	DU	DU	DU	AN	KW	KW

Female No.	Urine volume mL/24hr	S.G.	Electrolyte, density			Electrolyte, gross volume		
			Na	K	Cl	Na	K	Cl
			mEq/L	mEq/L	mEq/L	mEq/24hr	mEq/24hr	mEq/24hr
F04072	18.8	1.028	54.4	60.02	42.2	1.02	1.13	0.79
F04073	24.7	1.026	59.1	67.25	46.2	1.46	1.66	1.14
F04074	20.8	1.032	72.0	151.17	86.1	1.50	3.14	1.79
F04075	47.9	1.010	17.2	20.27	6.9 ^b	0.82	0.97	0.33
F04076	24.4	1.036	92.1	169.57	104.3	2.25	4.14	2.54
Number of females	5	5	5	5	5	5	5	5
Mean	27.3	1.026	59.0	93.66	57.1	1.41	2.21	1.32
S.D.	11.8	0.010	27.5	63.81	38.5	0.55	1.38	0.87
Significance	**	**	**	**	**	NS	NS	NS
Statistical method	DT	DU	DU	DU	DU	AN	KW	KW

^b, The re-measurement was carried out after adding the standard solution for urine to the sample because the first measured value exceeded the lower limit of quantitation range.
 The re-measured value was employed as the measured value for the specimen.

S.G.: Specific gravity

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.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 6

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Hematological analysis of males

Control (vehicle: corn oil)																
Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M01001	860	15.6	45.7	53.1	18.1	34.1	106.4	13.3	13.4	139.3	13.8	0.9	0.1	5.1	80.1	3.54
M01002	883	16.3	46.9	53.1	18.5	34.8	91.6	12.4	13.3	115.2	10.8	1.0	0.1	2.6	85.5	2.72
M01003	843	15.2	45.1	53.5	18.0	33.7	89.3	15.5	14.8	104.5	11.1	1.1	0.1	4.4	83.3	3.15
M01004	812	14.9	43.7	53.8	18.3	34.1	95.6	20.6	20.3	88.9	13.1	1.7	0.0	3.8	81.4	2.10
M01005	984	17.5	49.9	50.7	17.8	35.1	120.0	13.5	16.4	98.3	16.2	3.5	0.2	3.8	76.3	2.37
M01006	960	17.5	50.9	53.0	18.2	34.4	91.9	16.5	19.1	78.4	25.0	2.0	0.0	4.0	69.0	3.21
M01007	866	15.6	46.3	53.5	18.0	33.7	102.2	13.0	14.3	132.4	12.8	0.8	0.1	4.0	82.3	4.61
M01008	913	16.2	47.3	51.8	17.7	34.2	96.7	18.8	17.0	124.1	21.7	1.0	0.1	3.1	74.1	3.64
M01009	889	15.5	45.5	51.2	17.4	34.1	116.1	16.7	17.2	131.1	9.6	1.1	0.0	3.1	86.2	2.88
M01010	995	18.1	52.3	52.6	18.2	34.6	120.4	16.5	15.6	160.0	19.5	0.8	0.1	4.7	74.9	2.76
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	901	16.2	47.4	52.6	18.0	34.3	103.0	15.7	16.1	117.2	15.4	1.4	0.1	3.9	79.3	3.10
S.D.	61	1.1	2.8	1.0	0.3	0.5	12.1	2.7	2.3	25.0	5.1	0.8	0.1	0.8	5.6	0.72

Low dose (<i>p</i> -Cymene 12 mg/kg)																
Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
M02011	822	14.9	43.5	52.9	18.1	34.3	98.0	13.8	14.9	162.2	16.0	1.2	0.1	4.0	78.7	3.24
M02012	875	15.5	45.9	52.5	17.7	33.8	95.8	14.2	15.5	95.0	18.0	1.1	0.1	3.9	76.9	2.44
M02013	904	15.2	43.1	47.7	16.8	35.3	100.0	13.0	13.9	100.0	11.8	1.0	0.0	2.3	84.9	2.82
M02014	886	16.0	47.1	53.2	18.1	34.0	122.4	13.5	17.2	105.7	15.2	1.5	0.1	2.6	80.6	3.16
M02015	972	18.0	53.3	54.8	18.5	33.8	100.7	14.6	17.9	70.5	17.0	2.0	0.0	5.0	76.0	3.68
M02016	987	17.2	50.4	51.1	17.4	34.1	104.5	14.7	17.0	47.5	27.4	2.9	0.0	5.5	64.2	3.35
M02017	937	15.9	46.9	50.1	17.0	33.9	119.5	20.1	20.3	72.8	21.4	1.6	0.0	3.8	73.2	2.88
M02018	932	16.7	48.8	52.4	17.9	34.2	105.6	20.1	16.1	78.1	36.7	1.8	0.0	2.6	58.9	3.35
M02019	1003	18.1	52.2	52.0	18.0	34.7	122.2	13.3	13.4	114.7	22.9	1.5	0.1	3.4	72.1	3.24
M02020	1021	18.9	54.5	53.4	18.5	34.7	91.4	14.7	17.2	74.2	14.7	0.8	0.0	3.5	81.0	3.60
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	934	16.6	48.6	52.0	17.8	34.3	106.0	15.2	16.3	92.1	20.1	1.5	0.0	3.7	74.7	3.18
S.D.	63	1.4	4.0	2.0	0.6	0.5	11.4	2.6	2.0	31.7	7.4	0.6	0.1	1.0	8.0	0.37
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Appendix 6 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Hematological analysis of males

Medium dose (<i>p</i> -Cymene 60 mg/kg)																	
Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %	
M03021	839	14.4	41.6	49.6	17.2	34.6	93.2	16.1	19.7	94.8	11.8	1.2	0.1	4.0	82.9	3.06	
M03022	938	16.2	46.5	49.6	17.3	34.8	117.1	15.3	20.4	74.0	12.8	2.0	0.0	3.6	81.6	2.86	
M03023	874	15.6	45.7	52.3	17.8	34.1	106.6	12.3	13.4	87.5	15.3	0.9	0.1	4.3	79.4	2.73	
M03024	840	15.6	46.0	54.8	18.6	33.9	94.8	13.2	13.7	79.2	15.1	1.8	0.1	3.2	79.8	3.10	
M03025	916	17.2	51.1	55.8	18.8	33.7	103.5	12.8	15.3	66.9	14.6	3.1	0.1	3.6	78.6	3.61	
M03026	992	18.1	53.3	53.7	18.2	34.0	128.3	12.5	14.5	124.8	22.9	1.2	0.1	3.8	72.0	4.07	
M03027	832	14.8	43.4	52.2	17.8	34.1	115.2	15.7	14.8	99.1	13.3	1.6	0.0	1.7	83.4	3.89	
M03028	928	15.6	45.8	49.4	16.8	34.1	106.3	16.3	18.8	84.1	19.7	2.0	0.0	2.7	75.6	2.90	
M03029	882	15.0	44.1	50.0	17.0	34.0	126.0	15.2	13.1	144.8	16.3	0.7	0.1	4.2	78.7	3.42	
M03030	968	17.6	50.9	52.6	18.2	34.6	120.5	12.6	14.0	118.1	14.6	0.9	0.1	3.1	81.3	2.89	
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Mean	901	16.0	46.8	52.0	17.8	34.2	111.2	14.2	15.8	97.3	15.6	1.5	0.1	3.4	79.3	3.25	
S.D.	56	1.2	3.7	2.3	0.7	0.4	12.2	1.6	2.8	24.8	3.3	0.7	0.0	0.8	3.5	0.47	
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	DU	DU	DU	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	

High dose (<i>p</i> -Cymene 300 mg/kg)																	
Male No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %	
M04031	808	14.4	42.9	53.1	17.8	33.6	102.9	14.2	15.6	80.6	19.6	0.5	0.0	4.8	75.1	2.19	
M04032	864	14.6	43.1	49.9	16.9	33.9	101.3	12.9	16.0	201.2 #	14.8 #	0.3 #	0.0 #	2.7 #	82.2 #	3.53	
M04033	774	14.0	42.2	54.5	18.1	33.2	112.8	12.8	15.3	120.9	9.9	0.7	0.0	3.4	86.0	3.32	
M04034	914	15.5	45.3	49.6	17.0	34.2	103.9	11.7	14.5	77.0	27.7	1.0	0.0	5.1	66.2	2.99	
M04035	867	14.8	43.9	50.6	17.1	33.7	99.5	12.2	15.9	127.6	12.7	1.3	0.1	4.2	81.7	3.10	
M04036	815	14.6	43.5	53.4	17.9	33.6	105.3	11.2	12.5	90.0	16.0	1.9	0.0	4.8	77.3	3.07	
M04037	911	15.7	45.8	50.3	17.2	34.3	131.3	11.1	12.2	121.1	17.1	0.7	0.1	4.1	78.0	2.77	
M04038	819	14.2	42.2	51.5	17.3	33.6	102.5	11.1	12.3	108.0	28.0	0.6	0.0	2.8	68.6	2.96	
M04039	954	15.8	46.7	49.0	16.6	33.8	133.1	13.0	15.0	86.3	10.3	0.6	0.1	3.8	85.2	2.61	
M04040	804	13.6	41.3	51.4	16.9	32.9	95.6	23.3	17.3	96.8	12.8	1.0	0.0	3.2	83.0	2.98	
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Mean	853	14.7	43.7	51.3	17.3	33.7	108.8	13.4	14.7	111.0	16.9	0.9	0.0	3.9	78.3	2.95	
S.D.	59	0.7	1.7	1.8	0.5	0.4	13.1	3.6	1.8	36.4	6.5	0.5	0.0	0.9	6.7	0.37	
Significance	NS	*	*	NS	*	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	DU	DU	DU	AN	DU	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	

#, The first measured value was out of the control values stated in the standard operating procedures.

One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

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.

AN: Analysis by variance (one-way layout).

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Hematological analysis of females

Control (vehicle: corn oil)

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F01041	656	12.2	36.1	55.0	18.6	33.8	98.9	12.3	15.7	50.4	16.0	1.4	0.0	2.2	80.4	2.97
F01042	799	15.2	43.4	54.3	19.0	35.0	113.5	11.1	12.6	91.7	12.5	1.9	0.0	2.4	83.2	3.59
F01043	771	14.8	43.5	56.4	19.2	34.0	98.2	10.9	14.4	51.6	21.3	1.0	0.0	2.5	75.2	4.20
F01044	840	16.3	46.9	55.8	19.4	34.8	103.9	11.2	13.6	73.8	14.1	1.5	0.0	2.4	82.0	3.22
F01045	774	14.5	42.6	55.0	18.7	34.0	110.3	11.2	13.4	46.1	18.4	2.6	0.0	5.0	74.0	2.72
F01046	915	16.5	48.0	52.5	18.0	34.4	104.8	10.9	13.1	53.8	17.1	1.9	0.0	3.3	77.7	3.58
F01047	773	15.2	43.4	56.1	19.7	35.0	109.5	10.6	8.9	60.7	8.9	1.3	0.0	2.3	87.5	3.39
F01048	841	15.4	44.8	53.3	18.3	34.4	117.6	11.5	13.9	54.0	16.6	2.6	0.0	1.9	78.9	2.68
F01049	870	15.9	45.3	52.1	18.3	35.1	88.5	10.9	12.3	64.7	8.7	1.5	0.0	3.1	86.7	2.50
F01050	765	14.4	42.2	55.2	18.8	34.1	96.6	11.6	12.8	85.9	5.1	1.9	0.0	3.0	90.0	2.30
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	800	15.0	43.6	54.6	18.8	34.5	104.2	11.2	13.1	63.3	13.9	1.8	0.0	2.8	81.6	3.12
S.D.	71	1.2	3.2	1.5	0.5	0.5	8.8	0.5	1.8	15.7	5.0	0.5	0.0	0.9	5.3	0.59

Low dose (*p*-Cymene 12 mg/kg)

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F02051	715	13.8	39.4	55.1	19.3	35.0	85.3	10.6	12.5 §	65.4	10.1	1.4	0.0	2.3	86.2	2.94
F02052	733	14.0	40.5	55.3	19.1	34.6	90.2	11.4	11.5	65.0	11.1	1.5	0.0	2.8	84.6	2.60
F02053	691	13.6	39.1	56.6	19.7	34.8	80.6	11.1	9.3	58.8	16.6	1.2	0.2	3.9	78.1	2.22
F02054	818	15.8	45.3	55.4	19.3	34.9	99.4	11.0	14.7	75.3	7.6	1.3	0.0	3.6	87.5	2.89
F02055	787	14.9	43.5	55.3	18.9	34.3	100.5	11.1	12.7	68.3	12.2	2.2	0.0	1.9	83.7	3.38
F02056	852	15.2	43.5	51.1	17.8	34.9	108.1	11.1	13.7	57.7	10.1	1.9	0.0	2.4	85.6	1.95
F02057	823	15.3	43.9	53.3	18.6	34.9	88.3	11.1	12.5	72.2	10.4	1.1	0.0	2.8	85.7	2.47
F02058	856	16.0	47.1	55.0	18.7	34.0	101.9	10.7	9.6 §	54.4	6.3	1.8	0.0	2.4	89.5	2.21
F02059	863	15.3	44.7	51.8	17.7	34.2	100.2	11.3	12.0	54.0	11.5	2.2	0.0	2.8	83.5	2.74
F02060	830	16.1	47.1	56.7	19.4	34.2	88.5	11.1	14.3	59.5	10.1	0.8	0.0	2.2	86.9	2.56
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	797	15.0	43.4	54.6	18.9	34.6	94.3	11.1	12.3	63.1	10.6	1.5	0.0	2.7	85.1	2.60
S.D.	63	0.9	2.9	1.9	0.7	0.4	8.8	0.2	1.8	7.4	2.7	0.5	0.1	0.6	3.1	0.42
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	AN	AN	DU	AN	DU	KW	AN	KW	AN	AN	DU	DU

§, The sharp variation of the light scattering was not detected in the reaction in the first measurement.

The re-measurement was carried out and the sharp variation was observed in the reaction to give the acceptable value. The re-measured value was employed as the measured value for the specimen.

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DU: Analysis by Dunnett's test.

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Hematological analysis of females

Medium dose (*p*-Cymene 60 mg/kg)

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F03061	819	15.0	42.9	52.4	18.3	35.0	87.5	11.2	10.1	49.4	12.7	1.6	0.0	5.7	80.0	2.25
F03062	792	15.1	44.1	55.7	19.1	34.2	100.6	11.3	13.4	64.3	9.3	1.4	0.0	2.2	87.1	3.33
F03063	787	14.7	43.6	55.4	18.7	33.7	69.5	10.6	9.0 §	71.2	13.3	1.5	0.0	3.7	81.5	2.58
F03064	785	14.6	42.9	54.6	18.6	34.0	102.6	12.0	12.8	60.1	19.9	3.7	0.0	3.7	72.7	2.48
F03065	888	16.1	47.7	53.7	18.1	33.8	88.0	10.5	11.6	34.5	19.5	4.3	0.0	3.2	73.0	2.95
F03066	743	14.5	42.5	57.2	19.5	34.1	73.7	10.9	11.0	43.4	20.7	2.1	0.0	2.3	74.9	2.58
F03067	781	14.6	42.9	54.9	18.7	34.0	86.9	11.5	11.9	60.2	7.3	1.0	0.0	2.3	89.4	2.41
F03068	894	16.2	46.9	52.5	18.1	34.5	102.5	10.6	12.5	123.7	3.9	0.9	0.1	1.6	93.5	2.52
F03069	813	14.9	43.5	53.5	18.3	34.3	72.2	11.6	12.9	68.7	15.6	2.6	0.0	4.1	77.7	2.19
F03070	815	15.0	43.4	53.3	18.4	34.6	78.8	11.2	12.0	58.1	11.4	1.2	0.0	4.3	83.1	3.15
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	812	15.1	44.0	54.3	18.6	34.2	86.2	11.1	11.7	63.4	13.4	2.0	0.0	3.3	81.3	2.64
S.D.	47	0.6	1.8	1.5	0.4	0.4	12.6	0.5	1.4	24.1	5.6	1.2	0.0	1.2	7.1	0.38
Significance	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	KW	KW	AN	AN	AN	DU	AN	DU	KW	AN	KW	AN	AN	DU	DU

High dose (*p*-Cymene 300 mg/kg)

Female No.	RBC 10000/ μ L	HGB g/dL	Hematocrit %	MCV fL	MCH pg	MCHC g/dL	Platelet 10000/ μ L	PT sec.	APTT sec.	WBC 100/ μ L	Neutrophil %	Eosinophil %	Basophil %	Monocyte %	Lymphocyte %	Reticulocyte %
F04072	761	13.7	40.3	53.0	18.0	34.0	89.7	11.7	10.7	79.6	8.2	0.9	0.0	2.0	88.9	3.10
F04073	789	14.3	41.5	52.6	18.1	34.5	97.3	11.6	11.7	59.2	11.5	2.4	0.0	2.7	83.4	2.18
F04074	826	15.7	45.3	54.8	19.0	34.7	83.2	11.6	11.2	49.4	7.5	2.0	0.0	1.2	89.3	1.67
F04075	855	15.3	45.2	52.9	17.9	33.8	94.6	10.7	9.4	64.1	5.5	1.2	0.0	1.4	91.9	2.11
F04076	854	15.8	46.8	54.8	18.5	33.8	81.8	11.6	11.2	59.6	11.4	1.5	0.0	3.0	84.1	2.45
F04077	835	15.0	43.6	52.2	18.0	34.4	82.7	10.9	8.7	79.2	14.7	1.5	0.0	2.1	81.7	1.80
F04078	892	16.5	48.4	54.3	18.5	34.1	83.9	11.4	8.9	65.2	5.4	0.8	0.0	1.8	92.0	1.54
F04079	682	12.8	37.9	55.6	18.8	33.8	70.9	11.4	12.8	61.8	11.2	1.5	0.0	4.5	82.8	1.83
F04080	577	11.1	32.8	56.8	19.2	33.8	76.7	11.6	8.6	88.1	7.0	0.7	0.0	2.6	89.7	4.22
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	786	14.5	42.4	54.1	18.4	34.1	84.5	11.4	10.4	67.4	9.2	1.4	0.0	2.4	87.1	2.32
S.D.	100	1.7	4.9	1.5	0.5	0.4	8.3	0.4	1.5	12.3	3.2	0.6	0.0	1.0	4.1	0.85
Significance	NS	NS	NS	NS	NS	NS	**	NS	**	NS	NS	NS	NS	NS	NS	*
Statistical method	AN	KW	KW	AN	AN	AN	DU	AN	DU	KW	AN	KW	AN	AN	DU	DU

§, The sharp variation of the light scattering was not detected in the reaction in the first measurement.

The re-measurement was carried out and the sharp variation was observed in the reaction to give the acceptable value. The re-measured value was employed as the measured value for the specimen.

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).

DU: Analysis by Dunnett's test.

Appendix 7

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Blood biochemical analysis of males

Control (vehicle: corn oil)																		
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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
M01001	5.6	3.5	1.67	193	53	43	55	28	0	11.4	0.31	0.05	511	5.9	9.2	141.0	3.82	103.8
M01002	6.0	3.5	1.40	198	58	34	65	31	0	11.5	0.30	0.06	713	5.6	9.6	143.1	3.83	102.9
M01003	5.5	3.5	1.75	233	43	25	57	28	0	14.7	0.29	0.05	593	7.4	9.1	143.1	3.68	105.9
M01004	5.5	3.4	1.62	211	46	43	57	24	0	10.4	0.28	0.03	589	6.8	9.3	142.6	3.97	106.9
M01005	5.5	3.4	1.62	229	47	26	49	29	0	13.0	0.22	0.04	343	6.4	9.7	143.0	3.92	105.6
M01006	5.3	3.4	1.79	192	43	52	53	27	0	11.2	0.29	0.04	535	9.3	9.8	143.9	4.72	108.1
M01007	4.9	3.1	1.72	195	45	56	55	28	0	8.6	0.21	0.04	474	5.7	9.2	142.6	4.15	106.8
M01008	5.7	3.5	1.59	295	70	103	45	18	1	11.1	0.25	0.04	414	6.6	9.7	138.6	4.08	101.7
M01009	6.2	3.7	1.48	267	69	28	53	25	0	13.5	0.31	0.05	644	8.6	10.9	141.1	4.96	102.7
M01010	5.7	3.5	1.59	225	59	36	62	22	0	11.9	0.24	0.04	494	7.2	10.4	142.8	4.47	105.1
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.6	3.5	1.62	224	53	45	55	26	0	11.7	0.27	0.04	531	7.0	9.7	142.2	4.16	105.0
S.D.	0.4	0.2	0.12	34	10	23	6	4	0	1.7	0.04	0.01	109	1.2	0.6	1.5	0.42	2.1
Low dose (<i>p</i> -Cymene 12 mg/kg)																		
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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
M02011	5.9	3.5	1.46	255	67	78	64	28	0	10.9	0.23	0.04	527	6.0	9.8	141.2	3.90	103.7
M02012	5.2	3.3	1.74	244	40	50	51	27	0	10.1	0.27	0.05	487	6.8	9.4	139.5	4.98	107.3
M02013	5.4	3.4	1.70	271	54	31	60	32	0	12.2	0.22	0.05	522	6.4	9.9	139.8	4.33	103.7
M02014	6.2	3.8	1.58	297	61	51	46	26	0	11.2	0.31	0.03	526	6.8	10.3	142.1	4.77	105.6
M02015	5.2	3.2	1.60	238	52	36	45	23	0	15.5	0.30	0.04	526	8.3	9.7	139.6	4.92	104.3
M02016	5.9	3.6	1.57	277	69	23	63	33	0	13.4	0.26	0.04	603	7.1	10.4	144.0	4.40	107.8
M02017	5.5	3.3	1.50	206	50	48	49	30	0	11.3	0.24	0.03	505	6.7	9.5	141.4	4.13	105.2
M02018	5.0	3.1	1.63	317	53	25	48	24	0	14.4	0.29	0.03	385	7.9	9.3	138.9	4.96	103.8
M02019	6.1	3.8	1.65	334	55	81	56	34	0	11.9	0.32	0.04	397	7.9	10.5	140.9	4.06	100.8
M02020	5.8	3.2	1.23	249	68	35	47	30	0	18.4	0.79 #	0.04	489	14.9	10.1	140.8	6.23	98.3
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.6	3.4	1.57	269	57	46	53	29	0	12.9	0.32	0.04	497	7.9	9.9	140.8	4.67	104.1
S.D.	0.4	0.2	0.15	39	9	20	7	4	0	2.5	0.17	0.01	64	2.6	0.4	1.5	0.68	2.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	DU	AN	DT	DT	DT	AN	DU	KW	AN	AN	AN	KW	AN	AN	DU

#. The first measured value was out of the control values stated in the standard operating procedures.

One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 7 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Blood biochemical analysis of males

Medium dose (<i>p</i> -Cymene 60 mg/kg)																				
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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		
M03021	5.9	3.6	1.57	239	43	32	46	19	0	12.0	0.29	0.05	432	5.9	9.6	140.5	3.78	103.0		
M03022	6.2	3.9	1.70	353	51	43	61	33	0	10.0	0.25	0.04	715	6.1	9.8	140.1	4.39	101.9		
M03023	5.5	3.5	1.75	250	55	33	58	28	0	11.5	0.29	0.04	489	6.6	9.6	142.2	4.34	105.3		
M03024	5.6	3.5	1.67	245	47	11	58	26	0	16.2	0.31	0.04	405	7.9	10.1	141.5	5.27	104.8		
M03025	6.4	3.9	1.56	279	92	25	56	26	0	11.0	0.23	0.05	710	6.5	10.2	143.1	3.89	102.8		
M03026	6.1	3.3	1.18	342	68	41	49	31	1	15.4	0.50	0.04	766	11.9	10.1	137.3	6.71	98.9		
M03027	5.6	3.6	1.80	257	75	70	62	35	0	10.9	0.25	0.04	520	6.7	9.8	139.1 §	3.92 §	100.8 §		
M03028	5.3	3.3	1.65	369	43	37	49	21	0	13.0	0.26	0.04	495	8.1	9.6	138.6 §	5.22 §	100.4 §		
M03029	5.7	3.3	1.38	269	52	23	114	65 #	0	14.7	0.27	0.03	428	7.5	10.2	141.0	5.17	106.7		
M03030	5.6	3.3	1.43	237	50	28	60	25	0	15.0	0.41	0.04	488	10.7	10.1	142.9	4.93	103.9		
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
Mean	5.8	3.5	1.57	284	58	34	61	31	0	13.0	0.31	0.04	545	7.8	9.9	140.6	4.76	102.9		
S.D.	0.3	0.2	0.19	51	16	16	19	13	0	2.2	0.08	0.01	134	2.0	0.3	1.9	0.89	2.4		
Significance	NS	NS	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
Statistical method	AN	AN	DU	DU	AN	DT	DT	DT	AN	DU	KW	AN	AN	AN	KW	AN	AN	DU		

High dose (<i>p</i> -Cymene 300 mg/kg)																				
Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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		
M04031	5.8	3.7	1.76	252	41	26	81	38	0	12.0	0.31	0.04	816	6.6	9.6	140.0	3.69	101.5		
M04032	5.7	3.7	1.85	298	46	11	77	39	0	14.6	0.33	0.03	615	7.0	9.9	138.8 §	4.69 §	96.2 §		
M04033	5.3	3.5	1.94	308	37	13	94	49	0	12.3	0.28	0.03	501	6.4	9.9	141.1 §	4.14 §	102.4 §		
M04034	5.0	3.1	1.63	291	44	20	64	26	0	16.0	0.31	0.04	1006	7.7	9.5	139.0	4.69	102.1		
M04035	5.6	3.6	1.80	296	51	22	78	37	0	15.6	0.30	0.03	605	7.5	10.0	141.1 §	4.45 §	101.5 §		
M04036	5.3	3.5	1.94	241	60	23	57	29	0	13.9	0.30	0.04	429	6.9	10.3	142.6	4.66	104.3		
M04037	5.5	3.5	1.75	250	56	16	69	30	1	14.5	0.31	0.04	674	6.7	9.9	141.5 §	3.68 §	100.9 §		
M04038	5.3	3.2	1.52	293	56	15	55	29	0	18.8	0.38	0.05	481	8.2	9.8	143.8 §	4.37 §	105.8 §		
M04039	5.3	3.2	1.52	374	62	26	57	34	0	18.5	0.30	0.03	518	8.5	10.1	139.3 §	5.27 §	99.2 §		
M04040	5.5	3.6	1.89	361	57	27	70	43	0	22.0	0.45	0.04	604	10.4	10.3	138.0 §	5.17 §	98.9 §		
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		
Mean	5.4	3.5	1.76	296	51	20	70	35	0	15.8	0.33	0.04	625	7.6	9.9	140.5	4.48	101.3		
S.D.	0.2	0.2	0.16	44	9	6	13	7	0	3.1	0.05	0.01	174	1.2	0.3	1.8	0.54	2.7		
Significance	NS	NS	NS	**	NS	**	*	**	NS	**	NS	NS	NS	NS	NS	NS	NS	**		
Statistical method	AN	AN	DU	DU	AN	DT	DT	DT	AN	DU	KW	AN	AN	AN	KW	AN	AN	DU		

#. The first measured value was out of the control values stated in the standard operating procedures.

One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

§. The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.

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.

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 7 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Blood biochemical analysis of females

Control (vehicle: corn oil)																			
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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	
F01041	5.2	3.3	1.74	150	56	12	57	28	0	11.2	0.37	0.05	308	4.2	8.3	140.8	4.19	104.5	
F01042	5.5	3.5	1.75	165	67	25	50	22	0	15.1	0.36	0.04	333	6.6	8.7	139.5	4.95	105.3	
F01043	5.0	3.4	2.13	153	36	10	40	14	0	11.4	0.32	0.04	158	5.6	8.5	140.5	4.45	107.8	
F01044	5.0	3.4	2.13	153	44	19	53	20	0	14.7	0.42	0.04	341	6.4	8.4	139.1	4.36	102.6	
F01045	5.3	3.6	2.12	129	60	18	53	23	0	14.0	0.33	0.05	193	6.0	8.6	142.8	3.78	105.5	
F01046	5.1	3.2	1.68	163	50	11	55	21	0	12.4	0.33	0.04	344	10.4	8.4	144.5	5.38	108.5	
F01047	5.2	3.4	1.89	144	49	34	62	22	0	14.5	0.41	0.09	151	8.0	8.5	138.4	5.21	101.1	
F01048	5.4	3.4	1.70	204	52	15	47	17	0	9.7	0.37	0.05	295	9.0	8.8	139.6	4.94	102.7	
F01049	5.3	3.4	1.79	143	75	22	59	22	0	11.8	0.33	0.07	286	7.6	8.6	138.0	4.05	100.6	
F01050	5.6	3.5	1.67	154	65	15	55	26	0	11.0	0.35	0.05	226	8.6	9.0	142.1	4.23	102.2	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Mean	5.3	3.4	1.86	156	55	18	53	22	0	12.6	0.36	0.05	264	7.2	8.6	140.5	4.55	104.1	
S.D.	0.2	0.1	0.19	20	12	7	6	4	0	1.9	0.03	0.02	75	1.8	0.2	2.1	0.53	2.7	

Low dose (<i>p</i> -Cymene 12 mg/kg)																			
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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	
F02051	4.7	3.0	1.76	151	47	19	45	16	0	13.7	0.41	0.06	299	4.1	7.5	137.0	4.35	104.4	
F02052	5.5	3.6	1.89	155	68	25	54	32	1	15.0	0.37	0.04	276	6.2	8.8	138.5	4.42	102.4	
F02053	5.8	3.8	1.90	152	63	37	55	32	0	11.4	0.34	0.08	431	4.0	8.8	140.7	3.63	102.1	
F02054	5.3	3.5	1.94	124	58	18	45	19	0	15.7	0.33	0.07	194	7.6	8.7	141.4	4.59	106.6	
F02055	5.2	3.4	1.89	177	54	23	42	21	0	12.7	0.33	0.04	346	7.3	8.7	138.1	4.95	104.6	
F02056	5.6	3.4	1.55	127	54	12	70	42	0	16.1	0.33	0.04	375	9.1	9.0	145.5	4.79	108.1	
F02057	5.5	3.6	1.89	120	58	13	63	34	0	15.3	0.40	0.04	286	7.2	8.5	140.7	4.26	103.6	
F02058	5.0	3.3	1.94	116	68	35	48	19	0	15.5	0.43	0.06	314	9.5	9.0	139.1	5.19	102.0	
F02059	5.4	3.6	2.00	127	51	16	55	21	1	12.3	0.39	0.06	384	8.8	8.7	140.2	4.95	102.0	
F02060	5.1	3.2	1.68	128	48	18	54	18	0	9.6	0.28	0.04	281	6.3	8.0	141.6	3.63	103.8	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
Mean	5.3	3.4	1.84	138	57	22	53	25	0	13.7	0.36	0.05	319	7.0	8.6	140.3	4.48	104.0	
S.D.	0.3	0.2	0.14	20	8	9	9	9	0	2.2	0.05	0.01	68	1.9	0.5	2.4	0.53	2.1	
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Statistical method	AN	AN	AN	DU	AN	AN	AN	KW	DU	DT	DU	KW	AN	AN	AN	AN	AN	DT	

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).
 DT: Analysis by Dunnett type mean rank test.

Appendix 7 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Blood biochemical analysis of females

Medium dose (<i>p</i> -Cymene 60 mg/kg)																		
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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
F03061	4.9	3.3	2.06	192	48	33	50	18	1	11.6	0.29	0.05	225	5.9	7.9	137.4	4.20	102.9
F03062	5.0	3.3	1.94	169	55	17	51	20	1	11.8	0.28	0.05	246	5.3	8.3	140.1	4.00	103.6
F03063	5.3	3.4	1.79	140	68	18	57	21	1	14.2	0.33	0.05	372	6.8	8.5	138.4	4.48	101.1
F03064	5.7	3.3	1.38	153	71	17	63	23	1	16.0	0.39	0.05	365	7.3	8.7	139.9	4.49	101.2
F03065	5.5	3.6	1.89	163	74	13	57	19	1	9.2	0.31	0.05	328	7.8	8.6	140.2	4.67	101.6
F03066	5.8	3.6	1.64	220	60	17	65	20	2	11.8	0.35	0.04	258	9.7	8.9	143.5	5.84	102.2
F03067	5.1	3.3	1.83	147	66	21	51	17	1	15.5	0.37	0.05	227	6.8	8.6	141.9	4.24	103.2
F03068	5.0	3.1	1.63	177	63	19	49	16	1	12.4	0.32	0.05	238	7.0	8.5	140.4	4.14	103.1
F03069	5.4	3.6	2.00	163	48	12	56	18	1	10.4	0.26	0.05	271	8.0	8.8	140.4	4.67	101.7
F03070	5.6	3.7	1.95	183	65	24	56	16	0	11.2	0.32	0.06	221	6.5	8.7	137.3	4.27	98.7
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.3	3.4	1.81	171	62	19	56	19	1	12.4	0.32	0.05	275	7.1	8.6	140.0	4.50	101.9
S.D.	0.3	0.2	0.21	24	9	6	5	2	0	2.2	0.04	0.00	58	1.2	0.3	1.9	0.52	1.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	AN	AN	AN	KW	DU	DT	DU	KW	AN	AN	AN	AN	AN	DT

High dose (<i>p</i> -Cymene 300 mg/kg)																		
Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	AST U/L	ALT U/L	γ -GTP U/L	BUN 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
F04072	5.6	3.6	1.80	161	78	18	58	22	2	18.0	0.40	0.06	357	5.2	8.2	139.6	3.97	100.2
F04073	5.0	3.3	1.94	214	43	18	59	23	2	17.9	0.36	0.04	284	6.9	8.2	134.9	4.61	95.0
F04074	4.8	3.2	2.00	141	59	11	60	22	1	17.8	0.40	0.02	230	7.5	8.0	135.9	5.22	100.3
F04075	4.7	3.1	1.94	173	82	34	39	17	1	15.8	0.34	0.04	301	8.8	8.8	144.2	4.63	104.8
F04076	4.9	3.1	1.72	226	58	17	51	17	2	19.7	0.34	0.04	358	6.9	8.7	135.4	5.08	98.3
F04076	4.9	3.1	1.72	226	58	17	51	17	2	19.7	0.34	0.04	358	6.9	8.7	135.4	5.08	98.3
F04076	4.9	3.1	1.72	226	58	17	51	17	2	19.7	0.34	0.04	358	6.9	8.7	135.4	5.08	98.3
F04077	5.3	3.3	1.65	173	73	15	63	20	1	31.7	0.60 #	0.03	285	8.9	8.6	141.0	4.34	102.7
F04077	5.3	3.3	1.65	173	73	15	63	20	1	31.7	0.60 #	0.03	285	8.9	8.6	141.0	4.34	102.7
F04077	5.3	3.3	1.65	173	73	15	63	20	1	31.7	0.60 #	0.03	285	8.9	8.6	141.0	4.34	102.7
F04078	4.5	3.1	2.21	170	50	12	52	16	1	14.3	0.43	0.05	247	8.2	8.3	139.5	4.67	101.1
F04078	4.5	3.1	2.21	170	50	12	52	16	1	14.3	0.43	0.05	247	8.2	8.3	139.5	4.67	101.1
F04078	4.5	3.1	2.21	170	50	12	52	16	1	14.3	0.43	0.05	247	8.2	8.3	139.5	4.67	101.1
F04079	5.5	3.5	1.75	151	66	11	65	24	2	18.0	0.41	0.04	263	8.7	8.5	136.1	4.41	91.9
F04079	5.5	3.5	1.75	151	66	11	65	24	2	18.0	0.41	0.04	263	8.7	8.5	136.1	4.41	91.9
F04079	5.5	3.5	1.75	151	66	11	65	24	2	18.0	0.41	0.04	263	8.7	8.5	136.1	4.41	91.9
F04080	4.5	3.0	2.00	204	71	11	64	23	2	29.3	0.35	0.02	221	7.4	8.3	135.6	4.14	94.6
F04080	4.5	3.0	2.00	204	71	11	64	23	2	29.3	0.35	0.02	221	7.4	8.3	135.6	4.14	94.6
F04080	4.5	3.0	2.00	204	71	11	64	23	2	29.3	0.35	0.02	221	7.4	8.3	135.6	4.14	94.6
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	5.0	3.2	1.89	179	64	16	57	20	2	20.3	0.40	0.04	283	7.6	8.4	138.0	4.56	98.8
S.D.	0.4	0.2	0.18	29	13	7	8	3	1	6.0	0.08	0.01	50	1.2	0.3	3.2	0.41	4.2
Significance	NS	NS	NS	NS	NS	NS	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	**
Statistical method	AN	AN	AN	DU	AN	AN	AN	KW	DU	DT	DU	KW	AN	AN	AN	AN	AN	DT

#. The first measured value was out of the control values stated in the standard operating procedures.
 One re-measurement was carried out, and the difference between the values in two measurements was not more than 10% of the lower value. The first measured value was employed as the measured value for the specimen.

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).

DT: Analysis by Dunnett type mean rank test.

Appendix 8

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of males

Control (vehicle: corn oil)																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Lungs (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidney (mg)	
M01001	571.9	2195.8	3.839	285.9	0.500	1586.9	2.775	1598.6	2.795	14887.4	26.031	1867.6	3.266	1711.3	2.992	3578.9	6.258
M01002	551.7	1897.7	3.440	209.7	0.380	1535.3	2.783	1389.6	2.519	13210.4	23.945	1860.4	3.372	1739.3	3.153	3599.7	6.525
M01003	481.0	2064.2	4.291	269.2	0.560	1375.0	2.859	1564.7	3.253	11946.4	24.837	1520.6	3.161	1435.9	2.985	2956.5	6.147
M01004	499.9	1942.5	3.886	280.6	0.561	1386.7	2.774	1350.2	2.701	13916.8	27.839	1476.2	2.953	1475.7	2.952	2951.9	5.905
M01005	519.7	2011.2	3.870	198.6	0.382	1344.5	2.587	1451.0	2.792	12713.3	24.463	1612.6	3.103	1629.0	3.135	3241.6	6.237
M01006	414.4	2054.9	4.959	161.3	0.389	1117.5	2.697	1230.6	2.970	10944.4	26.410	1195.5	2.885	1192.9	2.879	2388.4	5.764
M01007	534.5	2048.8	3.833	323.1	0.604	1670.6	3.126	1847.8	3.457	14400.8	26.943	1842.3	3.447	1770.5	3.312	3612.8	6.759
M01008	619.9	2037.9	3.287	427.0	0.689	1656.2	2.672	2252.7	3.634	21174.8	34.158	1912.6	3.085	1947.7	3.142	3860.3	6.227
M01009	486.3	2074.1	4.265	285.6	0.587	1263.1	2.597	2046.8	4.209	13130.5	27.001	1493.1	3.070	1576.0	3.241	3069.1	6.311
M01010	560.3	2172.9	3.878	291.9	0.521	1563.0	2.790	1747.4	3.119	14960.2	26.700	1783.3	3.183	1826.3	3.260	3609.6	6.442
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	524.0	2050.0	3.955	273.3	0.517	1449.9	2.766	1647.9	3.145	14128.5	26.833	1656.4	3.153	1630.5	3.105	3286.9	6.258
S.D.	57.3	90.4	0.468	73.8	0.105	181.4	0.154	325.3	0.511	2784.5	2.858	234.4	0.174	219.4	0.146	447.3	0.287

Low dose (<i>p</i> -Cymene 12 mg/kg)																	
Male No.	Body weight (g)	Brain (mg)		Thymus (mg)		Heart (mg)		Lungs (mg)		Liver (mg)		Kidney (R) (mg)		Kidney (L) (mg)		Kidney (mg)	
M02011	621.5	2070.2	3.331	371.4	0.598	1779.9	2.864	1468.6	2.363	16542.5	26.617	1663.0	2.676	1589.4	2.557	3252.4	5.233
M02012	436.2	1861.4	4.267	350.4	0.803	1247.1	2.859	1183.0	2.712	11706.0	26.836	1644.1	3.769	1586.7	3.638	3230.8	7.407
M02013	578.1	1957.2	3.386	401.1	0.694	1916.5	3.315	1872.7	3.239	15315.8	26.493	2040.6	3.530	2054.2	3.553	4094.8	7.083
M02014	540.0	1794.2	3.323	201.2	0.373	1446.8	2.679	1422.9	2.635	15765.9	29.196	1511.2	2.799	1516.2	2.808	3027.4	5.606
M02015	479.9	2015.1	4.199	276.9	0.577	1396.8	2.911	2760.2	5.752	12293.1	25.616	1743.4	3.633	1742.3	3.631	3485.7	7.263
M02016	495.3	1950.9	3.939	257.6	0.520	1640.3	3.312	2041.0	4.121	15641.3	31.579	1549.0	3.127	1708.5	3.449	3257.5	6.577
M02017	507.8	1926.3	3.793	195.8	0.386	1307.8	2.575	1444.1	2.844	14477.7	28.511	1712.1	3.372	1737.7	3.422	3449.8	6.794
M02018	507.2	1964.0	3.872	445.4	0.878	1406.9	2.774	1285.6	2.535	16647.2	32.822	1821.9	3.592	1764.2	3.478	3586.1	7.070
M02019	601.5	1942.1	3.229	299.7	0.498	1483.8	2.467	1681.1	2.795	19450.0	32.336	1813.8	3.015	1888.9	3.140	3702.7	6.156
M02020	483.4	1939.0	4.011	186.4	0.386	1510.3	3.124	1603.2	3.317	12723.6	26.321	2049.0	4.239	2045.9	4.232	4094.9	8.471
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	525.1	1942.0	3.735	298.6	0.571	1513.6	2.888	1676.2	3.231	15056.3	28.633	1754.8	3.375	1763.4	3.391	3518.2	6.766
S.D.	59.0	75.4	0.387	91.2	0.176	209.0	0.289	460.6	1.020	2347.4	2.720	182.7	0.477	184.6	0.467	360.8	0.935
Significance	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	AN	AN	AN	AN	KW	KW	DU	DU	DU	DU	DU	DT	DU	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).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of males

Medium dose (<i>p</i> -Cymene 60 mg/kg)																	
Male No.	Body weight (g)	Brain		Thymus		Heart		Lungs		Liver		Kidney (R)		Kidney (L)		Kidney	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03021	478.0	1956.2	4.092	237.3	0.496	1335.5	2.794	1282.3	2.683	14560.0	30.460	1614.1	3.377	1589.7	3.326	3203.8	6.703
M03022	489.8	1975.4	4.033	168.1	0.343	1601.3	3.269	1439.2	2.938	15215.4	31.065	1703.2	3.477	1715.8	3.503	3419.0	6.980
M03023	517.4	1988.0	3.842	247.9	0.479	1477.5	2.856	1535.6	2.968	13565.5	26.219	1801.3	3.481	1818.1	3.514	3619.4	6.995
M03024	436.7	1999.6	4.579	199.7	0.457	1277.6	2.926	1503.3	3.442	12219.4	27.981	1594.4	3.651	1597.7	3.659	3192.1	7.310
M03025	582.6	1874.5	3.217	338.3	0.581	1620.4	2.781	1695.4	2.910	18326.5	31.456	2106.5	3.616	2164.6	3.715	4271.1	7.331
M03026	447.5	1901.6	4.249	213.4	0.477	1214.3	2.714	1505.6	3.364	15289.8	34.167	1897.7	4.241	1799.4	4.021	3697.1	8.262
M03027	547.6	1916.4	3.500	329.9	0.602	1430.7	2.613	1976.5	3.609	16507.0	30.144	1727.8	3.155	1651.4	3.016	3379.2	6.171
M03028	512.3	1948.2	3.803	463.3	0.904	1576.5	3.077	1538.0	3.002	16764.7	32.724	1607.9	3.139	1585.1	3.094	3193.0	6.233
M03029	566.2	1943.8	3.433	367.0	0.648	1620.7	2.862	1894.3	3.346	16877.4	29.808	1725.9	3.048	1694.5	2.993	3420.4	6.041
M03030	541.7	2007.1	3.705	197.1	0.364	1485.4	2.742	1524.5	2.814	14642.9	27.031	1980.6	3.656	1933.6	3.570	3914.2	7.226
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	512.0	1951.1	3.845	276.2	0.535	1464.0	2.863	1589.5	3.108	15396.9	30.106	1775.9	3.484	1755.0	3.441	3530.9	6.925
S.D.	49.0	43.5	0.409	94.3	0.162	147.5	0.190	209.5	0.307	1783.9	2.481	171.3	0.346	183.3	0.333	351.8	0.673
Significance	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS
Statistical method	AN	DU	AN	AN	AN	AN	AN	KW	KW	DU	DU	DU	DU	DU	DT	DU	DT

High dose (<i>p</i> -Cymene 300 mg/kg)																	
Male No.	Body weight (g)	Brain		Thymus		Heart		Lungs		Liver		Kidney (R)		Kidney (L)		Kidney	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04031	479.8	1920.1	4.002	200.0	0.417	1425.0	2.970	1508.9	3.145	19400.2	40.434	2115.8	4.410	2126.2	4.431	4242.0	8.841
M04032	476.5	1844.8	3.872	305.0	0.640	1533.0	3.217	1315.0	2.760	21020.2	44.114	1802.6	3.783	1928.9	4.048	3731.5	7.831
M04033	497.8	2057.8	4.134	275.8	0.554	1326.5	2.665	1623.3	3.261	23148.1	46.501	2143.3	4.306	2189.6	4.399	4332.9	8.704
M04034	419.6	1960.9	4.673	176.1	0.420	1152.0	2.745	1922.2	4.581	16938.1	40.367	1588.2	3.785	1636.5	3.900	3224.7	7.685
M04035	545.4	1967.6	3.608	323.8	0.594	1418.3	2.600	1415.5	2.595	23960.9	43.933	2174.6	3.987	2041.9	3.744	4216.5	7.731
M04036	520.5	1941.5	3.730	371.3	0.713	1454.2	2.794	1579.0	3.034	20098.8	38.614	2124.9	4.082	2042.8	3.925	4167.7	8.007
M04037	465.5	1910.4	4.104	335.8	0.721	1277.2	2.744	1744.3	3.747	19540.1	41.977	1601.5	3.440	1625.1	3.491	3226.6	6.931
M04038	462.3	1956.3	4.232	390.0	0.844	1220.0	2.639	1478.0	3.197	17369.4	37.572	1723.2	3.727	1602.0	3.465	3325.2	7.193
M04039	496.5	1919.8	3.867	206.3	0.416	1388.5	2.797	1382.1	2.784	21684.1	43.674	2235.2	4.502	2359.0	4.751	4594.2	9.253
M04040	452.1	1924.3	4.256	250.6	0.554	1279.5	2.830	1565.7	3.463	19597.9	43.349	1888.5	4.177	1796.6	3.974	3685.1	8.151
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	481.6	1940.4	4.048	283.5	0.587	1347.4	2.800	1553.4	3.257	20275.8	42.054	1939.8	4.020	1934.9	4.013	3874.6	8.033
S.D.	35.7	54.1	0.305	74.1	0.146	116.9	0.181	179.8	0.578	2254.7	2.774	248.4	0.338	262.3	0.413	501.8	0.729
Significance	NS	**	NS	NS	NS	NS	NS	NS	NS	**	**	*	**	**	**	**	**
Statistical method	AN	DU	AN	AN	AN	AN	AN	KW	KW	DU	DU	DU	DU	DU	DT	DU	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).

DU: Analysis by Dunnett's test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of males

Control (vehicle: corn oil)														
Male No.	Spleen		Testis (R)		Testis (L)		Testis		Prostate, ventral		Submandibular glands		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	956.6	1.673	1913.1	3.345	1906.4	3.333	3819.5	6.679	627.0	1.096	729.3	1.275	1744.2	3.050
M01002	740.0	1.341	1663.0	3.014	1680.3	3.046	3343.3	6.060	472.0	0.856	705.6	1.279	1282.1	2.324
M01003	654.5	1.361	1617.0	3.362	1613.1	3.354	3230.1	6.715	362.2	0.753	686.1	1.426	1713.2	3.562
M01004	837.5	1.675	1429.5	2.860	1436.4	2.873	2865.9	5.733	596.7	1.194	693.6	1.387	1988.3	3.977
M01005	775.2	1.492	1504.1	2.894	1537.3	2.958	3041.4	5.852	567.3	1.092	755.5	1.454	1511.4	2.908
M01006	654.2	1.579	1448.6	3.496	1502.5	3.626	2951.1	7.121	281.4	0.679	525.0	1.267	1348.9	3.255
M01007	1002.6	1.876	1622.8	3.036	1621.6	3.034	3244.4	6.070	618.1	1.156	655.9	1.227	1166.0	2.181
M01008	939.5	1.516	989.8	1.597	1738.4	2.804	2728.2	4.401	510.6	0.824	766.3	1.236	1655.7	2.671
M01009	853.2	1.754	1731.2	3.560	1736.5	3.571	3467.7	7.131	496.9	1.022	593.9	1.221	1403.2	2.885
M01010	781.9	1.396	1689.1	3.015	1623.0	2.897	3312.1	5.911	678.0	1.210	756.2	1.350	1487.1	2.654
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	819.5	1.566	1560.8	3.018	1639.6	3.150	3200.4	6.167	521.0	0.988	686.7	1.312	1530.0	2.947
S.D.	121.3	0.178	246.3	0.559	134.9	0.298	318.5	0.809	124.2	0.194	77.3	0.086	247.3	0.546

Low dose (<i>p</i> -Cymene 12 mg/kg)														
Male No.	Spleen		Testis (R)		Testis (L)		Testis		Prostate, ventral		Submandibular glands		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02011	936.1	1.506	1702.1	2.739	1701.5	2.738	3403.6	5.476	655.3	1.054	764.2	1.230	1645.5	2.648
M02012	743.8	1.705	1751.3	4.015	1720.6	3.945	3471.9	7.959	446.9	1.025	550.7	1.262	1177.1	2.699
M02013	999.2	1.728	1719.9	2.975	1726.8	2.987	3446.7	5.962	518.9	0.898	651.0	1.126	1343.0	2.323
M02014	716.7	1.327	1916.5	3.549	3083.6	5.710	5000.1	9.259	644.7	1.194	717.7	1.329	1551.3	2.873
M02015	795.4	1.657	1565.4	3.262	1578.9	3.290	3144.3	6.552	448.2	0.934	608.3	1.268	1136.0	2.367
M02016	803.9	1.623	1337.1	2.700	1433.4	2.894	2770.5	5.594	479.7	0.969	775.8	1.566	1409.6	2.846
M02017	890.9	1.754	1801.2	3.547	1754.5	3.455	3555.7	7.002	601.8	1.185	568.8	1.120	1596.0	3.143
M02018	795.9	1.569	1587.3	3.130	1617.3	3.189	3204.6	6.318	400.6	0.790	766.7	1.512	1746.8	3.444
M02019	1036.3	1.723	1790.5	2.977	1836.3	3.053	3626.8	6.030	715.6	1.190	827.6	1.376	1508.7	2.508
M02020	776.8	1.607	1837.8	3.802	1888.3	3.906	3726.1	7.708	557.0	1.152	679.9	1.406	1361.4	2.816
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	849.5	1.620	1700.9	3.270	1834.1	3.517	3535.0	6.786	546.9	1.039	691.1	1.320	1447.5	2.767
S.D.	109.8	0.129	166.6	0.446	457.7	0.869	583.8	1.204	105.1	0.141	94.8	0.149	198.7	0.344
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DT	DT	DT	DT	DT	DT	AN	AN	DU	AN	DU	DU

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of males

Male No.	Medium dose (<i>p</i> -Cymene 60 mg/kg)													
	Spleen		Testis (R)		Testis (L)		Testis		Prostate, ventral		Submandibular glands		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03021	901.5	1.886	1786.1	3.737	1731.9	3.623	3518.0	7.360	439.5	0.919	665.0	1.391	1252.9	2.621
M03022	685.2	1.399	1638.9	3.346	1559.6	3.184	3198.5	6.530	269.5	0.550	652.2	1.332	1567.4	3.200
M03023	751.9	1.453	1637.1	3.164	1656.9	3.202	3294.0	6.366	619.7	1.198	806.5	1.559	1552.0	3.000
M03024	619.6	1.419	1623.0	3.717	1607.4	3.681	3230.4	7.397	347.5	0.796	660.5	1.512	1300.6	2.978
M03025	1017.2	1.746	1477.3	2.536	1492.1	2.561	2969.4	5.097	588.6	1.010	800.9	1.375	2001.5	3.435
M03026	719.6	1.608	681.3	1.522	544.6	1.217	1225.9	2.739	383.0	0.856	622.1	1.390	1372.4	3.067
M03027	784.9	1.433	1456.2	2.659	1538.6	2.810	2994.8	5.469	485.8	0.887	701.8	1.282	1251.5	2.285
M03028	753.2	1.470	1562.5	3.050	1516.9	2.961	3079.4	6.011	586.2	1.144	808.7	1.579	1550.6	3.027
M03029	756.5	1.336	1441.0	2.545	1496.9	2.644	2937.9	5.189	616.4	1.089	664.9	1.174	1254.7	2.216
M03030	696.1	1.285	1674.4	3.091	1663.5	3.071	3337.9	6.162	841.6	1.554	712.1	1.315	1215.2	2.243
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	768.6	1.504	1497.8	2.937	1480.8	2.895	2978.6	5.832	517.8	1.000	709.5	1.391	1431.9	2.807
S.D.	114.1	0.188	306.5	0.658	338.5	0.696	642.5	1.348	166.9	0.271	70.7	0.128	243.8	0.435
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DT	DT	DT	DT	DT	DT	AN	AN	DU	AN	DU	DU

Male No.	High dose (<i>p</i> -Cymene 300 mg/kg)													
	Spleen		Testis (R)		Testis (L)		Testis		Prostate, ventral		Submandibular glands		Seminal vesicles	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04031	684.7	1.427	1000.4	2.085	1009.4	2.104	2009.8	4.189	364.0	0.759	558.2	1.163	1052.3	2.193
M04032	974.0	2.044	742.5	1.558	706.3	1.482	1448.8	3.041	365.6	0.767	680.5	1.428	1084.9	2.277
M04033	786.2	1.579	842.7	1.693	829.6	1.667	1672.3	3.359	555.3	1.116	640.6	1.287	1224.9	2.461
M04034	695.5	1.658	586.8	1.398	812.2	1.936	1399.0	3.334	345.8	0.824	637.4	1.519	930.2	2.217
M04035	824.9	1.512	871.7	1.598	907.6	1.664	1779.3	3.262	415.8	0.762	620.7	1.138	1296.1	2.376
M04036	933.3	1.793	850.3	1.634	867.7	1.667	1718.0	3.301	494.9	0.951	542.0	1.041	1171.2	2.250
M04037	621.7	1.336	760.6	1.634	700.0	1.504	1460.6	3.138	501.2	1.077	587.7	1.263	877.8	1.886
M04038	824.6	1.784	693.3	1.500	789.8	1.708	1483.1	3.208	603.9	1.306	598.4	1.294	975.6	2.110
M04039	854.6	1.721	944.6	1.903	727.8	1.466	1672.4	3.368	542.3	1.092	592.7	1.194	1360.5	2.740
M04040	732.3	1.620	817.3	1.808	837.4	1.852	1654.7	3.660	559.8	1.238	540.2	1.195	1145.2	2.533
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	793.2	1.647	811.0	1.681	818.8	1.705	1629.8	3.386	474.9	0.989	599.8	1.252	1111.9	2.304
S.D.	111.8	0.203	120.8	0.202	96.0	0.207	187.1	0.326	94.5	0.205	45.8	0.140	157.7	0.238
Significance	NS	NS	**	**	**	**	**	**	NS	NS	*	NS	**	**
Statistical method	AN	AN	DT	DT	DT	DT	DT	DT	AN	AN	DU	AN	DU	DU

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.

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of males

Control (vehicle: corn oil)											
Male No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	571.9	11.9	0.021	26.4	0.046	26.2	0.046	27.1	0.047	53.3	0.093
M01002	551.7	9.2	0.017	29.1	0.053	23.5	0.043	20.8	0.038	44.3	0.080
M01003	481.0	9.4	0.020	17.6	0.037	25.2	0.052	27.0	0.056	52.2	0.109
M01004	499.9	9.6	0.019	32.6	0.065	17.5	0.035	19.2	0.038	36.7	0.073
M01005	519.7	8.9	0.017	21.4	0.041	23.5	0.045	25.6	0.049	49.1	0.094
M01006	414.4	6.5	0.016	20.9	0.050	20.0	0.048	20.8	0.050	40.8	0.098
M01007	534.5	11.4	0.021	25.0	0.047	28.3	0.053	28.5	0.053	56.8	0.106
M01008	619.9	11.3	0.018	26.3	0.042	22.9	0.037	24.5	0.040	47.4	0.076
M01009	486.3	9.9	0.020	20.5	0.042	17.9	0.037	18.4	0.038	36.3	0.075
M01010	560.3	14.1	0.025	30.2	0.054	30.0	0.054	35.4	0.063	65.4	0.117
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	524.0	10.2	0.019	25.0	0.048	23.5	0.045	24.7	0.047	48.2	0.092
S.D.	57.3	2.1	0.003	4.8	0.008	4.2	0.007	5.2	0.009	9.2	0.016

Low dose (<i>p</i> -Cymene 12 mg/kg)											
Male No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02011	621.5	9.9	0.016	31.2	0.050	23.8	0.038	27.0	0.043	50.8	0.082
M02012	436.2	8.3	0.019	25.6	0.059	20.7	0.047	21.0	0.048	41.7	0.096
M02013	578.1	11.4	0.020	36.5	0.063	23.9	0.041	21.7	0.038	45.6	0.079
M02014	540.0	11.6	0.021	28.1	0.052	24.8	0.046	23.9	0.044	48.7	0.090
M02015	479.9	8.7	0.018	18.8	0.039	23.1	0.048	24.6	0.051	47.7	0.099
M02016	495.3	10.5	0.021	25.1	0.051	29.8	0.060	30.6	0.062	60.4	0.122
M02017	507.8	8.8	0.017	21.9	0.043	21.5	0.042	24.1	0.047	45.6	0.090
M02018	507.2	11.7	0.023	27.0	0.053	23.0	0.045	19.3	0.038	42.3	0.083
M02019	601.5	13.6	0.023	20.3	0.034	30.5	0.051	33.1	0.055	63.6	0.106
M02020	483.4	8.7	0.018	22.2	0.046	19.3	0.040	24.5	0.051	43.8	0.091
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	525.1	10.3	0.020	25.7	0.049	24.0	0.046	25.0	0.048	49.0	0.094
S.D.	59.0	1.7	0.002	5.4	0.009	3.6	0.006	4.3	0.007	7.4	0.013
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

NS: Not significantly different from the control group.
 AN: Analysis by variance (one-way layout).
 KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of males

Medium dose (<i>p</i> -Cymene 60 mg/kg)											
Male No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03021	478.0	8.3	0.017	22.2	0.046	21.4	0.045	22.1	0.046	43.5	0.091
M03022	489.8	8.5	0.017	21.7	0.044	17.8	0.036	21.4	0.044	39.2	0.080
M03023	517.4	10.5	0.020	21.0	0.041	22.2	0.043	25.8	0.050	48.0	0.093
M03024	436.7	7.7	0.018	26.3	0.060	19.0	0.044	21.6	0.049	40.6	0.093
M03025	582.6	9.7	0.017	27.0	0.046	29.7	0.051	32.4	0.056	62.1	0.107
M03026	447.5	8.8	0.020	18.2	0.041	17.8	0.040	21.4	0.048	39.2	0.088
M03027	547.6	9.5	0.017	31.1	0.057	16.8	0.031	18.9	0.035	35.7	0.065
M03028	512.3	10.6	0.021	28.5	0.056	21.2	0.041	21.5	0.042	42.7	0.083
M03029	566.2	10.8	0.019	28.7	0.051	21.5	0.038	21.6	0.038	43.1	0.076
M03030	541.7	8.4	0.016	24.4	0.045	22.2	0.041	24.3	0.045	46.5	0.086
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	512.0	9.3	0.018	24.9	0.049	21.0	0.041	23.1	0.045	44.1	0.086
S.D.	49.0	1.1	0.002	4.1	0.007	3.7	0.005	3.8	0.006	7.3	0.011
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

High dose (<i>p</i> -Cymene 300 mg/kg)											
Male No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04031	479.8	8.6	0.018	18.5	0.039	23.9	0.050	26.1	0.054	50.0	0.104
M04032	476.5	8.8	0.018	34.1	0.072	21.9	0.046	24.2	0.051	46.1	0.097
M04033	497.8	11.3	0.023	25.4	0.051	48.0	0.096	24.0	0.048	72.0	0.145
M04034	419.6	8.9	0.021	26.6	0.063	23.2	0.055	26.1	0.062	49.3	0.117
M04035	545.4	9.5	0.017	24.1	0.044	24.1	0.044	20.9	0.038	45.0	0.083
M04036	520.5	7.4	0.014	22.1	0.042	24.1	0.046	26.2	0.050	50.3	0.097
M04037	465.5	10.6	0.023	18.1	0.039	22.3	0.048	22.3	0.048	44.6	0.096
M04038	462.3	9.8	0.021	23.9	0.052	24.7	0.053	24.8	0.054	49.5	0.107
M04039	496.5	11.1	0.022	22.1	0.045	21.6	0.044	28.9	0.058	50.5	0.102
M04040	452.1	11.5	0.025	22.4	0.050	16.9	0.037	17.6	0.039	34.5	0.076
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	481.6	9.8	0.020	23.7	0.050	25.1	0.052	24.1	0.050	49.2	0.102
S.D.	35.7	1.4	0.003	4.5	0.011	8.4	0.016	3.2	0.008	9.4	0.019
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	AN

NS: Not significantly different from the control group.
 AN: Analysis by variance (one-way layout).
 KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females

Control (vehicle: corn oil)																	
Female No.	Body weight (g)	Brain (mg)		Thymus (mg/g)		Heart (mg)		Lungs (mg/g)		Liver (mg/g)		Kidney (R) (mg/g)		Kidney (L) (mg/g)		Kidney (mg/g)	
F01041	300.5	1953.3	6.500	281.8	0.938	920.0	3.062	1163.5	3.872	8063.2	26.833	1036.4	3.449	1052.5	3.502	2088.9	6.951
F01042	273.5	1858.1	6.794	318.3	1.164	867.8	3.173	1181.8	4.321	7024.3	25.683	953.3	3.486	926.7	3.388	1880.0	6.874
F01043	291.9	1746.7	5.984	292.0	1.000	959.3	3.286	1385.8	4.748	7702.8	26.388	1045.5	3.582	1005.7	3.445	2051.2	7.027
F01044	329.6	1853.1	5.622	380.2	1.154	920.9	2.794	1446.1	4.387	7889.3	23.936	994.4	3.017	1004.1	3.046	1998.5	6.063
F01045	267.5	1926.1	7.200	170.9	0.639	830.6	3.105	1104.4	4.129	7134.7	26.672	895.5	3.348	865.3	3.235	1760.8	6.582
F01046	257.1	1912.9	7.440	213.6	0.831	814.1	3.166	1011.6	3.935	7269.3	28.274	933.2	3.630	954.0	3.711	1887.2	7.340
F01047	280.9	1902.5	6.773	163.6	0.582	826.9	2.944	1085.6	3.865	7040.1	25.063	961.7	3.424	989.3	3.522	1951.0	6.946
F01048	279.9	1886.7	6.741	221.9	0.793	772.7	2.761	946.7	3.382	6996.0	24.995	919.2	3.284	894.3	3.195	1813.5	6.479
F01049	282.0	1832.8	6.499	184.4	0.654	880.4	3.122	1222.4	4.335	7372.7	26.144	993.9	3.524	1000.5	3.548	1994.4	7.072
F01050	288.5	1696.8	5.881	289.3	1.003	902.6	3.129	1052.5	3.648	7144.6	24.765	976.2	3.384	963.0	3.338	1939.2	6.722
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	285.1	1856.9	6.543	251.6	0.876	869.5	3.054	1160.0	4.062	7363.7	25.875	970.9	3.413	965.5	3.393	1936.5	6.806
S.D.	19.9	80.7	0.577	71.5	0.210	58.0	0.170	158.1	0.401	386.6	1.252	48.5	0.174	57.0	0.196	103.0	0.360

Low dose (<i>p</i> -Cymene 12 mg/kg)																	
Female No.	Body weight (g)	Brain (mg)		Thymus (mg/g)		Heart (mg)		Lungs (mg/g)		Liver (mg/g)		Kidney (R) (mg/g)		Kidney (L) (mg/g)		Kidney (mg/g)	
F02051	296.7	1828.1	6.161	183.4	0.618	1034.5	3.487	1277.6	4.306	8080.5	27.235	1231.2	4.150	1215.9	4.098	2447.1	8.248
F02052	299.7	1853.5	6.185	233.9	0.780	974.3	3.251	1155.1	3.854	7334.0	24.471	997.2	3.327	995.1	3.320	1992.3	6.648
F02053	296.2	1855.7	6.265	187.4	0.633	901.5	3.044	1175.0	3.967	8552.6	28.874	1083.6	3.658	1035.2	3.495	2118.8	7.153
F02054	283.2	1872.2	6.611	366.8	1.295	890.5	3.144	1161.7	4.102	7684.2	27.133	1002.4	3.540	1053.7	3.721	2056.1	7.260
F02055	302.5	1764.7	5.834	419.7	1.387	957.9	3.167	1513.8	5.004	8570.0	28.331	1058.7	3.509	1134.9	3.752	2193.6	7.252
F02056	263.7	1825.2	6.922	249.7	0.947	814.6	3.089	1088.2	4.127	6600.8	25.031	928.0	3.519	914.6	3.468	1842.6	6.987
F02057	271.8	1795.6	6.606	249.2	0.917	910.0	3.348	1154.0	4.246	7124.2	26.211	980.7	3.608	952.0	3.503	1932.7	7.111
F02058	263.7	1747.2	6.626	273.9	1.039	858.6	3.256	1784.3	6.766	7704.1	29.215	988.8	3.750	965.9	3.663	1954.7	7.413
F02059	287.5	1899.9	6.608	223.8	0.778	849.6	2.955	1075.5	3.741	7381.1	25.673	875.1	3.044	910.2	3.166	1785.3	6.210
F02060	247.9	1813.5	7.315	327.1	1.319	876.5	3.536	1083.6	4.371	6931.9	27.962	936.4	3.777	895.1	3.611	1831.5	7.388
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	281.3	1825.6	6.513	271.5	0.971	906.8	3.228	1246.9	4.448	7596.3	27.014	1008.2	3.587	1007.3	3.580	2015.5	7.167
S.D.	18.6	47.5	0.422	77.2	0.283	65.7	0.187	228.9	0.885	657.2	1.628	99.2	0.291	104.5	0.256	199.5	0.529
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	DU	AN	AN	AN	AN	DT	KW	DT	DT	KW	DU	KW	DU	KW	DU

NS: Not significantly different from the control group.
 DU: Analysis by Dunnett's test.
 AN: Analysis by variance (one-way layout).
 DT: Analysis by Dunnett type mean rank test.
 KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of females

Medium dose (<i>p</i> -Cymene 60 mg/kg)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Lungs		Liver		Kidney (R)		Kidney (L)		Kidney	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03061	296.2	1830.4	6.180	216.7	0.732	901.7	3.044	1067.5	3.604	8502.3	28.705	923.0	3.116	883.7	2.983	1806.7	6.100
F03062	277.3	1924.3	6.939	270.0	0.974	820.6	2.959	1109.7	4.002	8162.7	29.436	1174.4	4.235	1012.2	3.650	2186.6	7.885
F03063	270.4	1807.4	6.684	235.7	0.872	839.8	3.106	1086.8	4.019	8960.8	33.139	1012.6	3.745	982.7	3.634	1995.3	7.379
F03064	317.0	1835.0	5.789	213.3	0.673	933.4	2.944	1242.2	3.919	9516.2	30.020	1079.5	3.405	1018.8	3.214	2098.3	6.619
F03065	251.8	1747.1	6.938	199.2	0.791	901.4	3.580	1096.5	4.355	7728.5	30.693	907.0	3.602	939.5	3.731	1846.5	7.333
F03066	259.9	1729.5	6.654	214.6	0.826	771.8	2.970	1040.0	4.002	7830.5	30.129	975.2	3.752	907.6	3.492	1882.8	7.244
F03067	281.1	1916.8	6.819	247.8	0.882	821.9	2.924	1036.7	3.688	7402.7	26.335	912.5	3.246	863.7	3.073	1776.2	6.319
F03068	256.1	1640.6	6.406	418.6	1.635	782.0	3.053	1129.3	4.410	8710.9	34.014	903.5	3.528	864.0	3.374	1767.5	6.902
F03069	264.2	1801.2	6.818	250.4	0.948	978.9	3.705	1044.5	3.953	7770.4	29.411	1110.8	4.204	1085.4	4.108	2196.2	8.313
F03070	338.6	1977.1	5.839	195.9	0.579	961.8	2.841	1195.6	3.531	10470.2	30.922	1147.2	3.388	1167.5	3.448	2314.7	6.836
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	281.3	1820.9	6.507	246.2	0.891	871.3	3.113	1104.9	3.948	8505.5	30.280	1014.6	3.622	972.5	3.471	1987.1	7.093
S.D.	28.2	100.8	0.434	65.1	0.288	74.0	0.290	68.3	0.289	946.6	2.168	105.9	0.373	100.8	0.334	199.8	0.682
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	**	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	DU	AN	AN	AN	AN	AN	DT	KW	DT	DT	KW	DU	KW	DU	KW

High dose (<i>p</i> -Cymene 300 mg/kg)																	
Female No.	Body weight (g)	Brain		Thymus		Heart		Lungs		Liver		Kidney (R)		Kidney (L)		Kidney	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04072	240.4	1814.4	7.547	336.4	1.399	715.0	2.974	1017.2	4.231	8075.0	33.590	918.6	3.821	861.5	3.584	1780.1	7.405
F04073	302.9	1805.7	5.961	239.6	0.791	971.1	3.206	1561.1	5.154	11673.6	38.539	1165.4	3.847	1186.1	3.916	2351.5	7.763
F04074	223.4	1709.2	7.651	239.0	1.070	777.0	3.478	955.2	4.276	9175.4	41.072	949.1	4.248	970.3	4.343	1919.4	8.592
F04075	218.9	1746.2	7.977	234.7	1.072	624.7	2.854	878.1	4.011	7512.9	34.321	850.5	3.885	828.5	3.785	1679.0	7.670
F04076	259.8	1854.1	7.137	222.0	0.855	915.0	3.522	1081.6	4.163	10892.0	41.925	1180.9	4.545	1221.9	4.703	2402.8	9.249
F04077	273.4	1827.0	6.683	175.8	0.643	860.6	3.148	1084.8	3.968	11152.1	40.790	1222.3	4.471	1191.8	4.359	2414.1	8.830
F04078	202.6	1679.6	8.290	214.4	1.058	794.8	3.923	922.0	4.551	8996.7	44.406	910.1	4.492	878.1	4.334	1788.2	8.826
F04079	237.9	1781.1	7.487	138.7	0.583	782.5	3.289	941.2	3.956	9346.2	39.286	1040.4	4.373	1074.6	4.517	2115.0	8.890
F04080	257.9	1785.7	6.924	217.7	0.844	845.6	3.279	958.3	3.716	12437.9	48.228	1311.2	5.084	1205.7	4.675	2516.9	9.759
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	246.4	1778.1	7.295	224.3	0.924	809.6	3.297	1044.4	4.225	9918.0	40.240	1060.9	4.307	1046.5	4.246	2107.4	8.554
S.D.	30.7	56.8	0.707	53.6	0.253	103.8	0.318	206.0	0.421	1688.6	4.583	163.6	0.412	163.3	0.396	323.4	0.785
Significance	**	NS	*	NS	NS	NS	NS	NS	NS	**	**	NS	**	NS	**	NS	**
Statistical method	DU	AN	DU	AN	AN	AN	AN	DT	KW	DT	DT	KW	DU	KW	DU	KW	DU

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.

AN: Analysis by variance (one-way layout).

DT: Analysis by Dunnett type mean rank test.

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females

Control (vehicle: corn oil)												
Female No.	Spleen		Ovary (R)		Ovary (L)		Ovary		Uterus		Submandibular glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01041	601.8	2.003	44.1	0.147	48.1	0.160	92.2	0.307	608.8	2.026	515.3	1.715
F01042	540.7	1.977	37.1	0.136	35.6	0.130	72.7	0.266	627.5	2.294	377.6	1.381
F01043	489.5	1.677	56.3	0.193	52.5	0.180	108.8	0.373	501.2	1.717	454.6	1.557
F01044	723.4	2.195	55.7	0.169	42.1	0.128	97.8	0.297	626.7	1.901	426.1	1.293
F01045	543.2	2.031	41.1	0.154	44.9	0.168	86.0	0.321	514.3	1.923	510.3	1.908
F01046	516.0	2.007	54.6	0.212	43.1	0.168	97.7	0.380	462.7	1.800	479.4	1.865
F01047	442.0	1.574	41.9	0.149	37.3	0.133	79.2	0.282	431.7	1.537	426.2	1.517
F01048	516.6	1.846	34.3	0.123	39.9	0.143	74.2	0.265	1092.1	3.902	406.1	1.451
F01049	500.8	1.776	50.2	0.178	51.8	0.184	102.0	0.362	410.7	1.456	507.6	1.800
F01050	593.0	2.055	41.4	0.144	42.7	0.148	84.1	0.292	392.2	1.359	422.4	1.464
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	546.7	1.914	45.7	0.161	43.8	0.154	89.5	0.315	566.8	1.992	452.6	1.595
S.D.	77.9	0.191	8.0	0.027	5.7	0.021	12.2	0.043	204.4	0.727	48.4	0.213

Low dose (<i>p</i> -Cymene 12 mg/kg)												
Female No.	Spleen		Ovary (R)		Ovary (L)		Ovary		Uterus		Submandibular glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02051	758.0	2.555	48.2	0.162	32.7	0.110	80.9	0.273	438.1	1.477	476.8	1.607
F02052	538.0	1.795	54.2	0.181	54.1	0.181	108.3	0.361	459.8	1.534	560.0	1.869
F02053	702.2	2.371	30.6	0.103	40.2	0.136	70.8	0.239	727.2	2.455	496.1	1.675
F02054	517.4	1.827	40.2	0.142	34.3	0.121	74.5	0.263	388.6	1.372	412.5	1.457
F02055	610.8	2.019	46.6	0.154	45.2	0.149	91.8	0.303	588.7	1.946	418.8	1.384
F02056	524.6	1.989	55.1	0.209	43.0	0.163	98.1	0.372	404.0	1.532	409.3	1.552
F02057	514.9	1.894	47.8	0.176	47.3	0.174	95.1	0.350	432.6	1.592	512.6	1.886
F02058	592.3	2.246	47.7	0.181	43.3	0.164	91.0	0.345	590.5	2.239	504.4	1.913
F02059	510.8	1.777	33.3	0.116	46.6	0.162	79.9	0.278	422.0	1.468	495.9	1.725
F02060	531.4	2.144	44.6	0.180	32.0	0.129	76.6	0.309	865.9	3.493	421.9	1.702
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	580.0	2.062	44.8	0.160	41.9	0.149	86.7	0.309	531.7	1.911	470.8	1.677
S.D.	86.8	0.263	8.0	0.032	7.1	0.024	12.0	0.046	159.6	0.664	52.1	0.181
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	DU	AN	AN	DU	AN

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of females

Medium dose (<i>p</i> -Cymene 60 mg/kg)												
Female No.	Spleen		Ovary (R)		Ovary (L)		Ovary		Uterus		Submandibular glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03061	386.4	1.305	29.2	0.099	40.4	0.136	69.6	0.235	457.2	1.544	413.8	1.397
F03062	612.5	2.209	51.8	0.187	51.2	0.185	103.0	0.371	883.1	3.185	436.5	1.574
F03063	571.5	2.114	53.7	0.199	30.2	0.112	83.9	0.310	404.7	1.497	446.5	1.651
F03064	706.0	2.227	36.1	0.114	45.6	0.144	81.7	0.258	694.4	2.191	515.7	1.627
F03065	419.1	1.664	34.9	0.139	32.4	0.129	67.3	0.267	302.2	1.200	426.8	1.695
F03066	419.1	1.613	34.5	0.133	45.4	0.175	79.9	0.307	538.2	2.071	333.3	1.282
F03067	438.9	1.561	40.2	0.143	32.4	0.115	72.6	0.258	732.7	2.607	412.7	1.468
F03068	554.9	2.167	41.9	0.164	37.8	0.148	79.7	0.311	500.0	1.952	396.6	1.549
F03069	604.9	2.290	56.9	0.215	53.8	0.204	110.7	0.419	422.0	1.597	408.4	1.546
F03070	575.3	1.699	43.9	0.130	41.6	0.123	85.5	0.253	1011.6	2.988	450.7	1.331
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	528.9	1.885	42.3	0.152	41.1	0.147	83.4	0.299	594.6	2.083	424.1	1.512
S.D.	106.1	0.352	9.2	0.038	8.1	0.031	13.9	0.058	228.2	0.666	46.2	0.139
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	DU	AN	AN	DU	AN

High dose (<i>p</i> -Cymene 300 mg/kg)												
Female No.	Spleen		Ovary (R)		Ovary (L)		Ovary		Uterus		Submandibular glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04072	503.4	2.094	32.7	0.136	27.6	0.115	60.3	0.251	692.9	2.882	371.4	1.545
F04073	537.7	1.775	26.9	0.089	29.2	0.096	56.1	0.185	389.8	1.287	358.6	1.184
F04074	485.1	2.171	32.2	0.144	29.0	0.130	61.2	0.274	391.8	1.754	380.1	1.701
F04075	422.7	1.931	21.1	0.096	15.1	0.069	36.2	0.165	177.5	0.811	348.7	1.593
F04076	526.4	2.026	40.0	0.154	42.1	0.162	82.1	0.316	377.2	1.452	469.8	1.808
F04077	487.2	1.782	35.8	0.131	27.2	0.099	63.0	0.230	326.1	1.193	460.3	1.684
F04078	446.4	2.203	30.8	0.152	25.2	0.124	56.0	0.276	337.4	1.665	344.4	1.700
F04079	399.4	1.679	34.5	0.145	29.7	0.125	64.2	0.270	433.7	1.823	442.4	1.860
F04080	516.2	2.002	35.0	0.136	37.1	0.144	72.1	0.280	364.9	1.415	347.3	1.347
Number of females	9	9	9	9	9	9	9	9	9	9	9	9
Mean	480.5	1.963	32.1	0.131	29.1	0.118	61.2	0.250	387.9	1.587	391.4	1.602
S.D.	47.9	0.185	5.5	0.023	7.5	0.028	12.5	0.048	135.3	0.577	51.3	0.217
Significance	NS	NS	**	NS	**	*	**	*	NS	NS	*	NS
Statistical method	AN	AN	DU	AN	DU	DU	DU	DU	AN	AN	DU	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.

AN: Analysis by variance (one-way layout).

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females

Control (vehicle: corn oil)											
Female No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01041	300.5	11.9	0.040	20.5	0.068	33.2	0.110	40.0	0.133	73.2	0.244
F01042	273.5	16.8	0.061	20.2	0.074	24.8	0.091	27.1	0.099	51.9	0.190
F01043	291.9	14.2	0.049	12.8	0.044	35.0	0.120	31.1	0.107	66.1	0.226
F01044	329.6	12.5	0.038	24.7	0.075	33.1	0.100	35.7	0.108	68.8	0.209
F01045	267.5	13.5	0.050	19.2	0.072	33.3	0.124	32.8	0.123	66.1	0.247
F01046	257.1	13.1	0.051	16.0	0.062	25.9	0.101	28.6	0.111	54.5	0.212
F01047	280.9	17.5	0.062	17.0	0.061	30.0	0.107	30.0	0.107	60.0	0.214
F01048	279.9	14.0	0.050	18.9	0.068	21.1	0.075	27.1	0.097	48.2	0.172
F01049	282.0	14.8	0.052	16.2	0.057	44.3	0.157	45.5	0.161	89.8	0.318
F01050	288.5	14.2	0.049	24.0	0.083	28.3	0.098	30.4	0.105	58.7	0.203
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	285.1	14.3	0.050	19.0	0.066	30.9	0.108	32.8	0.115	63.7	0.224
S.D.	19.9	1.8	0.008	3.7	0.011	6.5	0.022	6.0	0.019	12.1	0.040

Low dose (<i>p</i> -Cymene 12 mg/kg)											
Female No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02051	296.7	14.8	0.050	19.5	0.066	33.8	0.114	37.3	0.126	71.1	0.240
F02052	299.7	12.8	0.043	18.0	0.060	30.1	0.100	35.2	0.117	65.3	0.218
F02053	296.2	15.2	0.051	18.0	0.061	38.6	0.130	44.5	0.150	83.1	0.281
F02054	283.2	15.7	0.055	17.7	0.063	35.5	0.125	36.8	0.130	72.3	0.255
F02055	302.5	17.3	0.057	23.0	0.076	24.3	0.080	26.2	0.087	50.5	0.167
F02056	263.7	11.1	0.042	15.7	0.060	24.9	0.094	27.3	0.104	52.2	0.198
F02057	271.8	11.0	0.040	15.9	0.058	36.7	0.135	38.2	0.141	74.9	0.276
F02058	263.7	13.4	0.051	16.5	0.063	26.8	0.102	30.6	0.116	57.4	0.218
F02059	287.5	12.0	0.042	18.2	0.063	31.0	0.108	28.0	0.097	59.0	0.205
F02060	247.9	13.1	0.053	16.6	0.067	38.1	0.154	39.2	0.158	77.3	0.312
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	281.3	13.6	0.048	17.9	0.064	32.0	0.114	34.3	0.123	66.3	0.237
S.D.	18.6	2.1	0.006	2.1	0.005	5.4	0.022	6.0	0.023	11.1	0.044
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN

NS: Not significantly different from the control group.
 DU: Analysis by Dunnett's test.
 AN: Analysis by variance (one-way layout).

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Organ weight of females

Medium dose (<i>p</i> -Cymene 60 mg/kg)											
Female No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03061	296.2	9.9	0.033	10.6	0.036	27.3	0.092	26.9	0.091	54.2	0.183
F03062	277.3	15.8	0.057	19.1	0.069	24.8	0.089	30.0	0.108	54.8	0.198
F03063	270.4	13.4	0.050	15.2	0.056	26.4	0.098	28.3	0.105	54.7	0.202
F03064	317.0	14.1	0.044	18.2	0.057	27.8	0.088	34.2	0.108	62.0	0.196
F03065	251.8	10.9	0.043	13.2	0.052	31.3	0.124	30.8	0.122	62.1	0.247
F03066	259.9	10.8	0.042	19.0	0.073	32.0	0.123	30.1	0.116	62.1	0.239
F03067	281.1	14.5	0.052	16.0	0.057	27.4	0.097	28.4	0.101	55.8	0.199
F03068	256.1	13.1	0.051	17.9	0.070	30.6	0.119	31.7	0.124	62.3	0.243
F03069	264.2	11.8	0.045	20.5	0.078	28.1	0.106	31.8	0.120	59.9	0.227
F03070	338.6	14.6	0.043	22.5	0.066	32.2	0.095	39.2	0.116	71.4	0.211
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	281.3	12.9	0.046	17.2	0.061	28.8	0.103	31.1	0.111	59.9	0.215
S.D.	28.2	1.9	0.007	3.5	0.012	2.6	0.014	3.5	0.010	5.3	0.023
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	AN	AN	AN	AN	AN	AN	AN	AN

High dose (<i>p</i> -Cymene 300 mg/kg)											
Female No.	Body weight (g)	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04072	240.4	11.4	0.047	12.7	0.053	20.7	0.086	21.5	0.089	42.2	0.176
F04073	302.9	8.8	0.029	17.5	0.058	26.2	0.086	30.5	0.101	56.7	0.187
F04074	223.4	9.7	0.043	19.6	0.088	29.3	0.131	27.5	0.123	56.8	0.254
F04075	218.9	6.8	0.031	13.7	0.063	19.0	0.087	21.3	0.097	40.3	0.184
F04076	259.8	8.5	0.033	16.3	0.063	35.0	0.135	36.0	0.139	71.0	0.273
F04077	273.4	12.5	0.046	16.3	0.060	28.7	0.105	30.9	0.113	59.6	0.218
F04078	202.6	8.8	0.043	16.7	0.082	24.5	0.121	22.7	0.112	47.2	0.233
F04079	237.9	13.3	0.056	19.8	0.083	31.7	0.133	38.0	0.160	69.7	0.293
F04080	257.9	12.5	0.048	13.8	0.054	32.1	0.124	33.7	0.131	65.8	0.255
Number of females	9	9	9	9	9	9	9	9	9	9	9
Mean	246.4	10.3	0.042	16.3	0.067	27.5	0.112	29.1	0.118	56.6	0.230
S.D.	30.7	2.2	0.009	2.5	0.013	5.3	0.021	6.3	0.022	11.4	0.042
Significance	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	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.

DU: Analysis by Dunnett's test.

AN: Analysis by variance (one-way layout).

Appendix 8 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Organ weight of females (sacrificed animal)

High dose (<i>p</i> -Cymene 300 mg/kg)																	
Female No.	Body	Brain		Thymus		Heart		Lungs		Liver		Kidney (R)		Kidney (L)		Kidney	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04071	170.2	1824.3	10.719	132.7	0.780	664.4	3.904	781.5	4.592	13718.6	80.603	1073.2	6.306	1016.2	5.971	2089.4	12.276

Female No.	Spleen		Ovary (R)		Ovary (L)		Ovaries		Uterus		Submandibular glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04071	124.5	0.731	27.8	0.163	39.0	0.229	66.8	0.392	272.4	1.600	318.8	1.873

Female No.	Pituitary gland		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04071	6.9	0.041	11.1	0.065	51.8	0.304	56.9	0.334	108.7	0.639

Appendix 9

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of males

Study No. : ██████
Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01001	All organs/	Within normal limits	
M01002	Liver/	Nodule	Whitish, Right medial lobe
M01003	All organs/	Within normal limits	
M01004	All organs/	Within normal limits	
M01005	All organs/	Within normal limits	
M01006	All organs/	Within normal limits	
M01007	All organs/	Within normal limits	
M01008	Adipose tissue/ Epididymis/ Lung/ Testis/	Nodule Small Discoloration, dark reddish Edematous Small	Yellowish, Around the spermatic cord, Right side Right side Right side Right side
M01009	All organs/	Within normal limits	
M01010	All organs/	Within normal limits	

Appendix 9 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Macroscopic findings of males

Study No. : ██████████
 Sex : MALE

Group 2 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M02011	All organs/	Within normal limits	
M02012	All organs/	Within normal limits	
M02013	All organs/	Within normal limits	
M02014	All organs/	Within normal limits	
M02015	Lung/	Incomplete retention	
M02016	All organs/	Within normal limits	
M02017	All organs/	Within normal limits	
M02018	All organs/	Within normal limits	
M02019	All organs/	Within normal limits	
M02020	All organs/	Within normal limits	

Appendix 9 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Macroscopic findings of males

Study No. : ██████████
 Sex : MALE

Group 3 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M03021	All organs/	Within normal limits	
M03022	All organs/	Within normal limits	
M03023	Liver/	Whitish area	Right medial lobe
M03024	All organs/	Within normal limits	
M03025	All organs/	Within normal limits	
M03026	Testis/	Edematous Small	Bilateral Bilateral
M03027	All organs/	Within normal limits	
M03028	All organs/	Within normal limits	
M03029	All organs/	Within normal limits	
M03030	Kidney/	Enlargement	Bilateral

Appendix 9 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Macroscopic findings of males

Study No. : ██████████
 Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04031	Kidney/ Testis/	Whitish area Small	Left side Bilateral
M04032	Kidney/ Liver/ Testis/	Enlargement Enlargement Edematous Small	Bilateral Bilateral Bilateral
M04033	Kidney/ Liver/ Testis/	Enlargement Discoloration, dark colored Enlargement Edematous Small	Bilateral Bilateral Bilateral
M04034	Epididymis/ Testis/	Small Edematous Small	Bilateral Bilateral Bilateral
M04035	Liver/ Spleen/ Stomach/ Testis/	Enlargement Recessed area Attachment, black substance Small	Mucosa, Glandular stomach Bilateral
M04036	Epididymis/ Testis/	Small Edematous Small	Bilateral Bilateral Bilateral
M04037	Epididymis/ Testis/	Small Edematous Small	Bilateral Bilateral Bilateral
M04038	Epididymis/ Liver/ Testis/	Small Enlargement Edematous Small	Bilateral Bilateral Bilateral

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of males

Study No. : [REDACTED]
 Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04039	Epididymis/ Kidney/ Testis/	Nodule Small Enlargement Edematous Small	Yellowish white, Cauda, Right side Bilateral Bilateral Bilateral Bilateral
M04040	Testis/	Small	Bilateral

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of females

Study No. : ██████████
 Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01041	All organs/	Within normal limits	
F01042	All organs/	Within normal limits	
F01043	All organs/	Within normal limits	
F01044	Kidney/	Cyst	Right side
F01045	All organs/	Within normal limits	
F01046	All organs/	Within normal limits	
F01047	All organs/	Within normal limits	
F01048	All organs/	Within normal limits	
F01049	All organs/	Within normal limits	
F01050	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of females

Study No. : ██████████
Sex : FEMALE

Group 6 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F02051	All organs/	Within normal limits	
F02052	All organs/	Within normal limits	
F02053	All organs/	Within normal limits	
F02054	All organs/	Within normal limits	
F02055	All organs/	Within normal limits	
F02056	All organs/	Within normal limits	
F02057	All organs/	Within normal limits	
F02058	Lung/	Dark reddish spot/area	Scattered
F02059	All organs/	Within normal limits	
F02060	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of females

Study No. : ██████████
 Sex : FEMALE

Group 7 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F03061	Spleen/	Small	
F03062	Liver/	Discoloration, dark colored	
F03063	All organs/	Within normal limits	
F03064	All organs/	Within normal limits	
F03065	All organs/	Within normal limits	
F03066	Stomach/	Reddish area	Mucosa, Glandular stomach
F03067	Liver/	Diaphragmatic nodule	
F03068	Liver/	Whitish area	Right medial lobe
F03069	All organs/	Within normal limits	
F03070	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of females

Study No. : ██████████
 Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04072	Stomach/	Attachment, black substance	Mucosa, Glandular stomach
F04073	All organs/	Within normal limits	
F04074	All organs/	Within normal limits	
F04075	Liver/ Spleen/	Discoloration, dark colored Small	
F04076	All organs/	Within normal limits	
F04077	All organs/	Within normal limits	
F04078	All organs/	Within normal limits	
F04079	All organs/	Within normal limits	
F04080	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Macroscopic findings of females (sacrificed animal)

Study No. : ██████████
 Sex : FEMALE

Group 8 : High dose

Stage : Moribund sacrifice

Animal No.	Organs	Findings	Notes
F04071	Adrenal gland/ External appearance/ Ileum/ Jejunum/ Liver/ Spleen/ Stomach/ Thymus/	Enlargement Emaciation Soiled fur Dark reddish area Dark reddish area Accentuated lobular pattern Enlargement Small Retention, gas Small	Bilateral Perineal region

Appendix 10

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]

Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01001	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Unilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
		Mineralization ±	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell ±	Alveolus
		Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
		Fatty change, hepatocyte 2+	Periportal
	Kidney /	Mineralization ±	Cortex, Unilateral
		Nephropathy, chronic progressive ±	
	Spleen /	Deposit, pigment, brown +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Infiltration, fatty ±	Diffuse
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01001	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Cellular infiltration, lymphocyte ±	Interstitial, Unilateral
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M01002	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte +	Interstitial, Unilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinata
	Zyngal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01002	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte +	Periportal
	Kidney /	Mineralization ±	Cortex, Unilateral
	Spleen /	Nephropathy, chronic progressive ±	
		Deposit, pigment, brown +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Infiltration, fatty ±	Diffuse
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Within normal limits	
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group I : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01003	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Within normal limits	
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Cellular infiltration, lymphocyte ±	Submucosa
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M01004	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Aberrant craniopharyngeal tissue P	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01004	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate +	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell ± Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Mineralization + Nephropathy, chronic progressive ±	Urothelium, Renal pelvis, Unilateral
	Spleen /	Deposit, pigment, brown ± Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Within normal limits	
	Prostate /	Cellular infiltration, lymphocyte ±	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE Group 1 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01006	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
M01007	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Cellular infiltration, lymphocyte ± Nephropathy, chronic progressive ±	Interstitial, Bilateral
Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary 2+		
Pancreas /	Within normal limits		
Adrenal gland /	Within normal limits		
Stomach /	Within normal limits		
Duodenum /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████
Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01007	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular ±	Bilateral
	Epididymis /	Cell debris ±	Lumen, Bilateral
	Prostate /	Atrophy ±	Focal
		Cellular infiltration, lymphocyte ±	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M01008	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Mineralization ±	Cornea, Unilateral
	Harderian gland /	Porphyrin secretion, increased ±	Bilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinata
		Mineralization +	Lamina propria mucosa, Ethmoturbinata
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE

Group 1 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01008	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Edema +	Pulmonary
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Cellular infiltration, lymphocyte ±	Interstitial, Bilateral
	Spleen /	Nephropathy, chronic progressive + Deposit, pigment, brown + Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema + Hyperplasia, Leydig cell ±	Unilateral Interstitial, Unilateral Diffuse, Bilateral
	Epididymis /	Cell debris + Reduced sperm 3+	Lumen, Unilateral Lumen, Unilateral
	Prostate /	Cellular infiltration, lymphocyte ±	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE Group 1 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01008	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
	Adipose tissue /	Cellular infiltration, mononuclear cell ± Fibrosis + Necrosis, fat 2+	Around the fat necrosis Around the fat necrosis Focal
M01009	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Edema ± Hemorrhage ±	Pulmonary Focal
	Bronchus /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE

Group I : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01009	Liver /	Fatty change, hepatocyte +	Periportal
	Kidney /	Dilatation, tubule, diffuse ±	Distal tubule, Cortex, Bilateral
	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Within normal limits	
	Prostate /	Cellular infiltration, lymphocyte +	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Stemum /	Degeneration, chondromucinous ±	Growth plate
Marrow, sternum /	Within normal limits		
Skeletal muscle /	Within normal limits		
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M01010	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE Group 1 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01010	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell ±	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte +	Periportal
	Kidney /	Dilatation, tubule, diffuse ±	Distal tubule, Cortex, Bilateral
		Nephropathy, chronic progressive ±	
	Spleen /	Deposit, pigment, brown +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Within normal limits	
	Epididymis /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
 Sex : MALE

Group I : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M01010	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous +	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group 2 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M02011	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte 2+ Necrosis, focal ± Within normal limits Within normal limits Within normal limits	Periportal
M02012	Liver / Kidney / Testis / Epididymis /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Centrilobular Periportal
M02013	Liver / Kidney / Testis / Epididymis /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte + Tension lipidosis P Cellular infiltration, lymphocyte ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Centrilobular Periportal Interstitial, Unilateral
M02014	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte 2+ Nephropathy, chronic progressive ± Dilatation, tubular 2+ Within normal limits	Periportal Diffuse, Unilateral
M02015	Lung / Bronchus / Liver / Kidney / Testis / Epididymis /	Within normal limits Within normal limits Fatty change, hepatocyte + Necrosis, focal ± Dilatation, tubule, diffuse ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Periportal Distal tubule, Cortex, Bilateral

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. [REDACTED]

Sex : MALE

Group 2 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M02016	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte 2+ Single cell necrosis, centrilobular ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Periportal, Centrilobular Hepatocyte
M02017	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte + Focus of cellular alteration ± Tension lipodosis P Mineralization ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Periportal Eosinophilic, Hepatocyte Medulla, Unilateral
M02018	Liver / Kidney / Testis / Epididymis /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Cellular infiltration, lymphocyte ± Nephropathy, chronic progressive ± Within normal limits Cellular infiltration, lymphocyte ±	Centrilobular Periportal Interstitial, Bilateral Interstitial, Bilateral
M02019	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte 2+ Dilatation, tubule, diffuse ± Mineralization ± Nephropathy, chronic progressive ± Within normal limits Cellular infiltration, lymphocyte ±	Periportal Distal tubule, Cortex, Bilateral Cortex, Unilateral Interstitial, Unilateral
M02020	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Necrosis, focal ± Tension lipodosis P Congestion ± Dilatation, tubule, diffuse ±	Centrilobular Periportal Papillary tip, Bilateral Distal tubule, Cortex, Bilateral

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group 2 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M02020	Kidney / Testis / Epididymis /	Nephropathy, chronic progressive 2+ Within normal limits Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]

Sex : MALE

Group 3 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M03021	Liver / Kidney / Testis / Epididymis /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ± Hyaline droplet ± Within normal limits Within normal limits	Centrilobular Periportal Centrilobular, With eosinophilic change Hepatocyte Papillary epithelium, Papillary duct, Unilateral
M03022	Liver / Kidney / Testis / Epididymis /	Within normal limits Dilatation, tubule, diffuse ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Distal tubule, Cortex, Bilateral
M03023	Liver / Kidney / Testis / Epididymis /	Cellular infiltration, mononuclear cell ± Single cell necrosis, centrilobular ± Tension lipodosis P Within normal limits Within normal limits Within normal limits	Centrilobular Hepatocyte
M03024	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte ± Hypertrophy, hepatocellular ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Periportal Centrilobular, With eosinophilic change
M03025	Liver / Kidney / Testis / Epididymis /	Fatty change, hepatocyte ± Hypertrophy, hepatocellular ± Single cell necrosis, centrilobular ± Mineralization ± Nephropathy, chronic progressive ± Within normal limits Within normal limits	Periportal Centrilobular, With eosinophilic change Hepatocyte Cortex, Bilateral

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE Group 3 : Medium dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M03026	Liver / Kidney /	Fatty change, hepatocyte ± Dilatation, tubule, diffuse ± Nephropathy, chronic progressive 2+	Periportal Distal tubule, Cortex, Bilateral
	Testis /	Degeneration/atrophy, tubular 3+ Edema 2+ Hyperplasia, Leydig cell 2+	Bilateral Interstitial, Bilateral Diffuse, Bilateral
	Epididymis /	Cell debris 2+ Reduced sperm 2+	Lumen, Bilateral Lumen, Bilateral
M03027	Liver / Kidney /	Fatty change, hepatocyte ± Dilatation, tubule, diffuse ± Mineralization ±	Periportal Distal tubule, Cortex, Bilateral Papilla, Unilateral
	Testis / Epididymis /	Within normal limits Within normal limits	
M03028	Liver / Kidney /	Fatty change, hepatocyte + Dilatation, tubule, diffuse ± Nephropathy, chronic progressive ±	Periportal Distal tubule, Cortex, Bilateral
	Testis / Epididymis /	Degeneration/atrophy, tubular ± Within normal limits	Unilateral
M03029	Liver /	Fatty change, hepatocyte + Hypertrophy, hepatocellular ± Single cell necrosis, centrilobular ±	Periportal, Centrilobular Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Dilatation, tubule, diffuse ± Mineralization ± Nephropathy, chronic progressive ±	Distal tubule, Cortex, Bilateral Medulla, Bilateral
	Testis / Epididymis /	Within normal limits Within normal limits	
M03030	Liver /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Single cell necrosis, centrilobular ±	Centrilobular Periportal, Centrilobular Hepatocyte
	Kidney /	Congestion ±	Papillary tip, Bilateral

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]
Sex : MALE

Group 3 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M03030	Kidney / Testis / Epididymis /	Dilatation, tubule, diffuse + Nephropathy, chronic progressive 2+ Within normal limits Within normal limits	Distal tubule, Cortex, Bilateral

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of males

Study No. : ██████████
 Sex : MALE Group 4 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04031	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Mineralization ±	Cornea, Unilateral
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
		Hypertrophy, hepatocellular +	Centrilobular, With eosinophilic change
		Single cell necrosis, centrilobular ±	Hepatocyte
	Kidney /	Congestion ±	Papillary tip, Bilateral
		Dilatation, tubule, diffuse ±	Distal tubule, Cortex, Bilateral
		Dilatation, tubule, focal +	Cortex, Unilateral
		Hyaline droplet ±	Papillary epithelium, Unilateral
		Nephropathy, chronic progressive ±	
		Vacuolation, cytoplasmic +	Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04031	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema + Hyperplasia, Leydig cell ±	Bilateral Interstitial, Bilateral Diffuse, Bilateral
	Epididymis /	Cell debris 2+ Reduced sperm 2+ Atrophy ±	Lumen, Bilateral Lumen, Bilateral Focal
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04032	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Cyst P	Anterior lobe
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
	Zymbal gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04032	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, pigment, brown ±	Kupffer cell, Centrilobular
		Hypertrophy, hepatocellular 2+	Centrilobular, With eosinophilic change
		Single cell necrosis, centrilobular +	Hepatocyte
	Kidney /	Dilatation, tubule, diffuse +	Distal tubule, Cortex, Bilateral
		Nephropathy, chronic progressive ±	
		Vacuolation, cytoplasmic +	Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 3+	Bilateral
		Edema 2+	Interstitial, Bilateral
		Hyperplasia, Leydig cell 2+	Diffuse, Bilateral

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████
Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04032	Epididymis /	Cell debris 2+	Lumen, Bilateral
		Reduced sperm 2+	Lumen, Bilateral
	Prostate /	Cellular infiltration, lymphocyte +	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
M04033	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell ±	Alveolus

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04034	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema 2+ Hyperplasia, Leydig cell +	Bilateral Interstitial, Bilateral Diffuse, Bilateral
	Epididymis /	Cell debris 2+ Reduced sperm 2+	Lumen, Bilateral Lumen, Bilateral
	Prostate /	Within normal limits	
	Seminal vesicle /	Atrophy +	Bilateral
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04035	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04035	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell + Hemorrhage ±	Alveolus Focal
	Bronchus /	Within normal limits	
	Liver /	Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ± Tension lipidosis P	Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Congestion ± Dilatation, tubule, diffuse + Mineralization ± Necrosis, papillary ± Nephropathy, chronic progressive ± Vacuolation, cytoplasmic +	Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Papilla, Unilateral Tip, Bilateral
	Spleen /	Deposit, pigment, brown + Fibrosis, focal ± Hematopoiesis, extramedullary 2+	Collecting duct, Outer zone of the inner medulla, Bilateral Capsule, Recessed area
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04035	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema ± Hyperplasia, Leydig cell +	Bilateral Interstitial, Bilateral Diffuse, Bilateral
	Epididymis /	Cell debris 3+ Reduced sperm 2+	Lumen, Bilateral Lumen, Bilateral
	Prostate /	Cellular infiltration, lymphocyte +	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
M04036	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04036	Sublingual gland / Tongue / Esophagus / Trachea / Aorta / Thyroid gland / Parathyroid gland / Thymus / Heart / Lung /	Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Not tissue Hyperplasia, epithelial ± Necrosis/inflammatory cell infiltrate ± Accumulation, foam cell ± Cellular infiltration, inflammatory ± Metaplasia, osseous ± Within normal limits	Medulla Cardiomyocyte, Focal Alveolus Periarterial, Focal Focal
	Bronchus / Liver /	Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ± Tension lipidosis P	Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Cellular infiltration, neutrophil ± Congestion + Dilatation, tubule, diffuse + Hyaline droplet ± Hyperplasia, transitional cell ± Necrosis, papillary + Nephropathy, chronic progressive ± Regeneration, tubule ± Vacuolation, cytoplasmic +	Papillary tip, Bilateral Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Papillary epithelium, Unilateral Focal, Papillary epithelium, Unilateral Tip, Bilateral Papilla, Unilateral Collecting duct, Outer zone of the inner medulla, Outer medulla, Bilateral
	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary +	
	Pancreas / Adrenal gland / Stomach / Duodenum / Jejunum / Ileum / Cecum /	Within normal limits Within normal limits Dilatation, gland ± Within normal limits Within normal limits Within normal limits Within normal limits	Focal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04036	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+	Bilateral
		Edema +	Interstitial, Bilateral
		Hyperplasia, Leydig cell ±	Diffuse, Bilateral
	Epididymis /	Cell debris 3+	Lumen, Bilateral
		Reduced sperm 2+	Lumen, Bilateral
	Prostate /	Atrophy ±	Focal
		Cellular infiltration, lymphocyte ±	Interstitial
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04037	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
		Mineralization ±	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████
Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04037	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate +	Cardiomyocyte, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ± Deposit, pigment, brown ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ±	Centrilobular Kupffer cell, Centrilobular Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Cellular infiltration, lymphocyte ± Congestion ± Dilatation, tubule, diffuse + Hyaline droplet ± Necrosis, papillary + Nephropathy, chronic progressive ± Vacuolation, cytoplasmic +	Interstitial, Bilateral Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Papillary epithelium, Papillary duct, Bilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown ± Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04037	Testis /	Degeneration/atrophy, tubular 2+	Bilateral
		Edema 2+	Interstitial, Bilateral
		Hyperplasia, Leydig cell +	Diffuse, Bilateral
	Epididymis /	Cell debris 2+	Lumen, Bilateral
		Reduced sperm 3+	Lumen, Bilateral
	Prostate /	Within normal limits	
	Seminal vesicle /	Atrophy ±	Bilateral
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04038	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]
Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04038	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell ±	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ±	Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Cellular infiltration, neutrophil ± Congestion ± Dilatation, tubule, diffuse ± Necrosis, papillary + Vacuolation, cytoplasmic ±	Papillary tip, Bilateral Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema + Hyperplasia, Leydig cell +	Bilateral Interstitial, Bilateral Diffuse, Bilateral
	Epididymis /	Cell debris 2+ Reduced sperm 3+	Lumen, Bilateral Lumen, Bilateral
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : ██████████

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04039	Liver /	Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ± Tension lipodosis P	Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Cellular infiltration, lymphocyte ± Congestion ± Dilatation, tubule, diffuse + Hyaline droplet + Hyperplasia, transitional cell ± Mineralization ± Necrosis, papillary + Nephropathy, chronic progressive + Vacuolation, cytoplasmic +	Interstitial, Unilateral Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Papillary duct, Bilateral Focal, Papillary epithelium, Unilateral Papilla, Unilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 3+ Edema 2+ Hyperplasia, Leydig cell + Cell debris 2+	Bilateral Interstitial, Bilateral Diffuse, Bilateral Lumen, Bilateral
	Epididymis /	Granuloma, spermatic + Reduced sperm 2+	Unilateral Lumen, Bilateral
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04039	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
M04040	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Hyperplasia, anterior lobe ±	Focal
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate +	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell ±	Alveolus
		Metaplasia, osseous ±	Focal
Bronchus /	Within normal limits		
Liver /	Hypertrophy, hepatocellular 2+	Centrilobular, With eosinophilic change	
	Single cell necrosis, centrilobular ±	Hepatocyte	
Kidney /	Cellular infiltration, neutrophil ±	Papillary tip, Bilateral	

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. : [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04040	Kidney /	Congestion ± Dilatation, tubule, diffuse 2+ Necrosis, papillary ± Nephropathy, chronic progressive ± Vacuolation, cytoplasmic ±	Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown + Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Testis /	Degeneration/atrophy, tubular 2+ Edema + Hyperplasia, Leydig cell ±	Bilateral Interstitial, Bilateral Diffuse, Bilateral Lumen, Bilateral Lumen, Bilateral
	Epididymis /	Cell debris 3+ Reduced sperm 2+	
	Prostate /	Within normal limits	
	Seminal vesicle /	Within normal limits	
	Coagulating gland /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of males

Study No. [REDACTED]

Sex : MALE

Group 4 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
M04040	Mammary gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████

Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01041	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Dysplasia, retina P	Unilateral
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Mineralization ±	Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte +	Periportal
	Kidney /	Mineralization ±	Medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary +	
	Pancreas /	Cellular infiltration, lymphocyte ±	Interstitial
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01041	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F01042	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules + Mineralization ±	Olfactory epithelium, Ethmoturbinat Lamina propria mucosa, Ethmoturbinat
	Zymal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████

Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01042	Lung /	Accumulation, foam cell ± Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
	Kidney /	Mineralization ± Nephropathy, chronic progressive ±	Medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+ Hematopoiesis, extramedullary ±	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
F01043	Brain /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01043	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Mineralization ±	Cornea, Unilateral
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Unilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinate
		Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Edema ±	Pulmonary
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Mineralization ±	Medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : █████

Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01043	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F01044	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Mineralization ±	Cornea, Bilateral
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Unilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ehmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Within normal limits	
	Lung /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 5 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01045	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Cellular infiltration, lymphocyte ±	Interstitial
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Fibrosis, myocardial ±	Focal, Apex
	Lung /	Accumulation, foam cell ±	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Within normal limits	
	Kidney /	Within normal limits	
	Spleen /	Deposit, pigment, brown 2+ Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
Colon /	Within normal limits		
Rectum /	Within normal limits		
Lymph node, submandibular /	Within normal limits		

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 5 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01045	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F01046	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ± Mineralization ±	Olfactory epithelium, Ethmoturbinat Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████

Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01046	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Mineralization ±	Medulla, Bilateral
	Spleen /	Deposit, pigment, brown +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F01047	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01047	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Mineralization ±	Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Mineralization ±	Medulla, Bilateral
	Spleen /	Deposit, pigment, brown 3+ Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01047	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F01048	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules + Mineralization ±	Olfactory epithelium, Ethmoturbinat Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01049	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Bilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
		Mineralization +	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
		Fatty change, hepatocyte ±	Periportal
		Mineralization ±	Medulla, Bilateral
		Nephropathy, chronic progressive ±	
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
Ileum /	Within normal limits		
Cecum /	Within normal limits		
Colon /	Within normal limits		
Rectum /	Within normal limits		

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. [REDACTED]
 Sex : FEMALE Group 5 : Control Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01049	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
F01050	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Bilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
Heart /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████
Sex : FEMALE

Group 5 : Control

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F01050	Lung /	Accumulation, foam cell ± Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Tension lipodosis P	Centrilobular, Periportal Periportal
	Kidney /	Dilatation, tubule, diffuse ±	Distal tubule, Cortex, Bilateral
	Spleen /	Deposit, pigment, brown 3+ Hematopoiesis, extramedullary ±	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE

Group 6 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F02051	Liver / Kidney /	Within normal limits Nephropathy, chronic progressive ±	
F02052	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Tension lipodosis P Dilatation, tubule, diffuse ± Mineralization +	Centrilobular Distal tubule, Cortex, Bilateral Medulla, Bilateral
F02053	Liver / Kidney /	Within normal limits Mineralization ±	Medulla, Bilateral
F02054	Liver / Kidney /	Fatty change, hepatocyte ± Mineralization ± Nephropathy, chronic progressive ±	Periportal Medulla, Bilateral
F02055	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Mineralization + Nephropathy, chronic progressive ±	Centrilobular Periportal Medulla, Bilateral
F02056	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Mineralization ±	Centrilobular Medulla, Bilateral
F02057	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Tension lipodosis P Mineralization ±	Centrilobular Periportal Medulla, Bilateral
F02058	Lung / Bronchus / Liver / Kidney /	Accumulation, foam cell ± Edema + Hemorrhage ± Within normal limits Fatty change, hepatocyte + Dilatation, tubule, diffuse ±	Alveolus Pulmonary Focal Periportal Distal tubule, Cortex, Bilateral

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE

Group 6 : Low dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F02058	Kidney /	Mineralization ± Nephropathy, chronic progressive ±	Medulla, Bilateral
F02059	Liver / Kidney /	Fatty change, hepatocyte + Mineralization ± Nephropathy, chronic progressive ±	Periportal Medulla, Bilateral
F02060	Liver / Kidney /	Fatty change, hepatocyte ± Within normal limits	Periportal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ████████
Sex : FEMALE

Group 7 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F03061	Liver / Kidney / Spleen /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Hypertrophy, hepatocellular ± Single cell necrosis, centrilobular ± Mineralization ± Deposit, pigment, brown 2+ Hematopoiesis, extramedullary +	Centrilobular Periportal Centrilobular, With eosinophilic change Hepatocyte Medulla, Bilateral
F03062	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Deposit, pigment, brown ± Hypertrophy, hepatocellular ± Single cell necrosis, centrilobular ± Tension lipodosis P Mineralization ± Nephropathy, chronic progressive ±	Centrilobular Kupffer cell, Centrilobular Centrilobular, With eosinophilic change Hepatocyte Medulla, Bilateral
F03063	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Deposit, pigment, brown ± Fatty change, hepatocyte ± Focus of cellular alteration ± Within normal limits	Centrilobular Kupffer cell, Centrilobular Periportal Eosinophilic, Hepatocyte
F03064	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Cellular infiltration, lymphocyte ± Mineralization ±	Centrilobular Interstitial, Unilateral Medulla, Bilateral
F03065	Liver / Kidney /	Fatty change, hepatocyte ± Tension lipodosis P Hyaline droplet ± Nephropathy, chronic progressive ±	Periportal Papillary duct, Unilateral
F03066	Liver / Kidney / Stomach /	Fatty change, hepatocyte ± Within normal limits Congestion ±	Periportal Focal, Glandular stomach

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE

Group 7 : Medium dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F03067	Liver / Kidney /	Fatty change, hepatocyte ± Nodule, hepatodiaphragmatic P Mineralization ±	Periportal With focal fibrosis Medulla, Bilateral
F03068	Liver / Kidney /	Fatty change, hepatocyte ± Tension lipidosis P Mineralization ± Nephropathy, chronic progressive ±	Periportal Medulla, Bilateral
F03069	Liver / Kidney /	Cellular infiltration, mononuclear cell ± Mineralization ±	Centrilobular Medulla, Bilateral
F03070	Liver / Kidney /	Fatty change, hepatocyte ± Hypertrophy, hepatocellular ± Dilatation, tubule, diffuse ± Hyaline droplet ± Mineralization ± Nephropathy, chronic progressive ±	Periportal Centrilobular, With eosinophilic change Distal tubule, Cortex, Bilateral Papillary epithelium, Papillary duct, Bilateral Medulla, Bilateral

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. [REDACTED]

Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04072	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Cyst P	Anterior lobe
	Eyeball /	Dysplasia, retina P	Unilateral
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ±	Olfactory epithelium, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Hemorrhage ±	Focal
		Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
		Hypertrophy, hepatocellular +	Centrilobular, With eosinophilic change
		Necrosis, focal ±	
		Single cell necrosis, centrilobular ±	Hepatocyte
	Kidney /	Mineralization ±	Medulla, Bilateral
		Vacuolation, cytoplasmic +	Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary ±	
	Pancreas /	Cellular infiltration, lymphocyte ±	Interstitial
	Adrenal gland /	Within normal limits	
Stomach /	Within normal limits		
Duodenum /	Within normal limits		
Jejunum /	Within normal limits		

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04072	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
F04073	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ± Mineralization ±	Olfactory epithelium, Ethmoturbinate Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████

Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04073	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Edema ± Hemorrhage ±	Pulmonary Focal
	Bronchus /	Within normal limits	
	Liver /	Deposit, pigment, brown ± Fatty change, hepatocyte ± Hypertrophy, hepatocellular ± Single cell necrosis, centrilobular ±	Kupffer cell, Centrilobular Periportal Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Congestion ± Dilatation, tubule, diffuse ± Necrosis, papillary ± Nephropathy, chronic progressive ± Vacuolation, cytoplasmic ±	Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Tip, Unilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 3+ Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04073	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F04074	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Not tissue	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell ± Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	Periportal
Liver /	Fatty change, hepatocyte ± Hypertrophy, hepatocellular + Tension lipodosis P	Centrilobular, With eosinophilic change	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████
 Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04074	Kidney /	Congestion ± Dilatation, tubule, diffuse ± Necrosis, papillary + Vacuolation, cytoplasmic + Deposit, pigment, brown 3+ Hematopoiesis, extramedullary + Decrease, zymogen granule +	Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /		
	Pancreas /		Acinar cell, Diffuse
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
F04075	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████

Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04075	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte ±	Interstitial, Bilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinate
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ±	Centrilobular
		Deposit, pigment, brown ±	Kupffer cell, Centrilobular
		Hypertrophy, hepatocellular +	Centrilobular, With eosinophilic change
		Single cell necrosis, centrilobular +	Hepatocyte
	Kidney /	Necrosis, papillary ±	Tip, Bilateral
		Vacuolation, cytoplasmic ±	Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+	
		Hematopoiesis, extramedullary ±	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04075	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Increased number, atretic follicle +	Bilateral
	Oviduct /	Within normal limits	
	Uterus /	Atrophy +	
	Vagina /	Mucinous degeneration ±	
	Urinary bladder /	Within normal limits	
	Femur /	Bone, decreased, trabecula +	Metaphysis, Bilateral
	Marrow, femur /	Hematopoiesis, decreased 2+	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Hematopoiesis, decreased +	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
F04076	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Cyst P	Anterior lobe
	Eyeball /	Dysplasia, retina P	Unilateral
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ± Mineralization ±	Olfactory epithelium, Ethmoturbinat Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : ██████████
Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04076	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell + Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ± Focus of cellular alteration ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ± Congestion ±	Centrilobular Eosinophilic, Hepatocyte Centrilobular, With eosinophilic change Hepatocyte Papillary tip, Bilateral
	Kidney /	Dilatation, tubule, diffuse ± Mineralization + Necrosis, papillary ± Nephropathy, chronic progressive ± Vacuolation, cytoplasmic ± Deposit, pigment, brown 2+	Distal tubule, Cortex, Bilateral Medulla, Bilateral Tip, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Hematopoiesis, extramedullary ±	
	Pancreas /	Within normal limits	
	Adrenal gland /	Hypertrophy, cortical cell +	Diffuse, Fascicular zone
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04077	Kidney /	Hyaline droplet ± Necrosis, papillary ± Regeneration, tubule ± Vacuolation, cytoplasmic + Deposit, pigment, brown 3+ Hematopoiesis, extramedullary +	Papillary epithelium, Papillary duct, Bilateral Tip, Bilateral Papilla, Bilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Within normal limits	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Degeneration, chondromucinous ±	Growth plate
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
Sciatic nerve /	Within normal limits		
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
F04078	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04078	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globules ± Mineralization ±	Olfactory epithelium, Ethmoturbinat Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Focus of cellular alteration ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ±	Centrilobular Periportal Eosinophilic, Hepatocyte Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Dilatation, tubule, diffuse ± Hyaline droplet ± Necrosis, papillary ± Nephropathy, chronic progressive ± Vacuolation, cytoplasmic ±	Distal tubule, Cortex, Bilateral Papillary epithelium, Unilateral Tip, Unilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+ Hematopoiesis, extramedullary ±	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04079	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial ±	Medulla
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ±	Periportal Centrilobular, With eosinophilic change Hepatocyte
	Kidney /	Congestion ± Dilatation, tubule, diffuse ± Hyaline droplet ± Mineralization + Necrosis, papillary + Regeneration, tubule ± Vacuolation, cytoplasmic +	Papillary tip, Bilateral Distal tubule, Cortex, Bilateral Papillary epithelium, Papillary duct, Bilateral Medulla, Papillary tip, Bilateral Tip, Bilateral Papilla, Unilateral Collecting duct, Outer zone of the inner medulla, Bilateral
	Spleen /	Deposit, pigment, brown 2+ Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Focus of vacuolation ±	Cortical cell, Glomerular zone, Fascicular zone
	Stomach /	Within normal limits	
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Within normal limits	
	Lymph node, submandibular /	Within normal limits	
	Lymph node, mesenteric /	Within normal limits	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	

Appendix 10 (Continued)
 Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females

Study No. : ██████████
 Sex : FEMALE Group 8 : High dose Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04079	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
F04080	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria mucosa, Ethmoturbinat
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
Liver /	Cellular infiltration, mononuclear cell ± Fatty change, hepatocyte ± Hypertrophy, hepatocellular + Single cell necrosis, centrilobular ±	Centrilobular Periportal Centrilobular, With eosinophilic change Hepatocyte	

Continued

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females

Study No. : [REDACTED]
Sex : FEMALE

Group 8 : High dose

Stage : Terminal sacrifice

Animal No.	Organs	Findings	Notes
F04080	Skin / Mammary gland /	Within normal limits Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats

Histopathological findings of females (sacrificed animal)

Study No. [REDACTED]

Sex : FEMALE

Group 8 : High dose

Stage : Moribund sacrifice

Animal No.	Organs	Findings	Notes
F04071	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Porphyrin secretion, increased 3+	Bilateral
	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zymlal gland /	Within normal limits	
	Submandibular gland /	Hypertrophy, acinar cell + Single cell necrosis ±	Diffuse Acinar cell, Diffuse
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	
	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Not tissue	
	Thymus /	Atrophy 2+	
	Heart /	Necrosis/inflammatory cell infiltrate ±	Cardiomyocyte, Focal
	Lung /	Accumulation, foam cell ± Mineralization ±	Alveolus Arterial wall
	Bronchus /	Within normal limits	
	Liver /	Hypertrophy, hepatocellular 2+ Single cell necrosis, centrilobular ± Vacuolation, cytoplasmic 3+	Diffuse Hepatocyte Hepatocyte, Periportal, Midzonal
	Kidney /	Cellular infiltration, neutrophil + Congestion + Dilatation, tubule, diffuse 3+ Hyaline droplet ± Mineralization ± Necrosis, papillary + Nephropathy, chronic progressive + Regeneration, tubule 2+ Vacuolation, cytoplasmic 2+	Papillary tip, Bilateral Papillary tip, Bilateral Distal tubule, Collecting duct, Cortex, Bilateral Papillary epithelium, Papillary duct, Bilateral Medulla, Bilateral Tip, Bilateral Papilla, Bilateral Collecting duct, Distal tubule, Proximal tubule, Outer zone of the inner medulla, Outer medulla, Cortex, Bilateral

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of *p*-Cymene in rats
 Histopathological findings of females (sacrificed animal)

Study No. [REDACTED]
 Sex : FEMALE

Group 8 : High dose

Stage : Moribund sacrifice

Animal No.	Organs	Findings	Notes
F04071	Spleen /	Atrophy 3+ Deposit, pigment, brown 2+	Red pulp, White pulp
	Pancreas /	Decrease, zymogen granule ±	Acinar cell, Diffuse
	Adrenal gland /	Vacuolation, cortical, increased +	Diffuse, Microvesicular
	Stomach /	Vacuolation, cytoplasmic +	Parietal cell, Microvesicular
	Duodenum /	Within normal limits	
	Jejunum /	Autolysis P	Focal
	Ileum /	Autolysis P Necrosis, lymphocyte +	Focal Peyer's patch
	Cecum /	Within normal limits	
	Colon /	Within normal limits	
	Rectum /	Decrease, mucin, goblet cell +	
	Lymph node, submandibular /	Atrophy +	
	Lymph node, mesenteric /	Atrophy +	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Necrosis, focal +	Metaphyseal area
	Sternum /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	

品質試験表

国立医薬品食品衛生研究所安全性生物試験研究センター 御中

品名	p-サイメン
ロット番号	
出荷日	
数量	5kg

試験項目	規格	試験成績	判定
比重 d20/4	0.854 ~ 0.858	0.856	適
屈折率 n20/D	1.489 ~ 1.492	1.4900	適
純度 (GC)	95 % 以上	98.5 %	適

総合判定	合格
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上記の品質であることを証明します。

品質試験責任者	試験担当者
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Annex 2

投与検体中の被験物質濃度測定法

1) 試薬

- ・ 蒸留水 (HPLC 用、和光純薬工業、ロット番号 [REDACTED])
- ・ アセトニトリル (HPLC 用、和光純薬工業、ロット番号 [REDACTED])
- ・ アセトン (HPLC 用、和光純薬工業、ロット番号 [REDACTED])

2) 試液の調製

(1) 移動相

アセトニトリル 800 mL および蒸留水 200 mL を混合した。

(2) 媒体の確認溶液

トウモロコシ油 1 mL を正確にとり、アセトンを加えて正確に 30 mL とした。この液 1 mL を正確にとり、アセトンを加えて正確に 10 mL として媒体の確認溶液とした。

3) 機器

- ・ 電子天秤 (R200D、ザルトリウス)
- ・ 高速液体クロマトグラフ (島津製作所)

構成: LC-10AT VP (ポンプ)、SCL-10A VP (システムコントローラ)、SIL-10AD VP (サンプルクーラー付オートインジェクタ)、CTO-10AS VP (カラムオーブン)、DGU-12A (デガッサ)、SPD-10A VP (検出器)、C-R7A plus (データ処理装置)

4) 標準溶液の調製

被験物質約 50 mg を精密に量りとり、アセトンを加えて正確に 10 mL とした。この液 1 mL を正確にとり、アセトンを加えて正確に 100 mL として標準原液とした。標準原液 1、2 および 4 mL を正確にとり、それぞれアセトンを加えて正確に 10 mL とし、標準溶液 (約 5、10 および 20 $\mu\text{g/mL}$ 、St 1~3) を調製した。標準溶液は各濃度 $n=1$ で調製した。

5) 試料溶液の調製

試料溶液の調製は、投与検体の採取からそれぞれ $n=3$ とした。

(1) 3 mg/mL 溶液

投与検体 1 mL を正確にとり、アセトンを加えて正確に 30 mL とした。この液 1 mL を正確にとり、アセトンを加えて正確に 10 mL として試料溶液を調製した (10.0 $\mu\text{g/mL}$ 、希釈率: 300)。

(2) 15 mg/mL 溶液

投与検体 1 mL を正確にとり、アセトンを加えて正確に 50 mL とした。この液 1 mL を正確にとり、アセトンを加えて正確に 30 mL として試料溶液を調製した (10.0 $\mu\text{g/mL}$ 、希釈率: 1500)。

(3) 75 mg/mL 溶液

投与検体 1 mL を正確にとり、アセトンを加えて正確に 250 mL とした。この液 1 mL を正確にとり、アセトンを加えて正確に 30 mL として試料溶液を調製した (10.0 $\mu\text{g/mL}$ 、希釈率: 7500)。

6) 投与検体中の被験物質の濃度測定法

標準溶液 (St 1~3) および試料溶液につき、それぞれ下記の測定条件で高速液体クロマトグラフィーにより試験を行った。標準溶液は各濃度 3 回ずつ、試料溶液はそれぞれ 1 回ずつ測定した。標準溶液の測定で得られた p -サイメンのピーク面積と調製濃度を基に、最小二乗法により検量線を作成した。作成した検量線を用いて試料溶液中の被験物質濃度を求め、これに希釈率を乗じて投与検体中の被験物質濃度を算出した。また、媒体の確認溶液を 1 回測定し、 p -サイメンのピーク保持時間付近に妨害ピークがないことを確認した。

HPLC 測定条件

検出器	紫外可視分光光度計検出器
分析カラム	CAPCELL PAK C18 MGII (内径 4.6 mm、長さ 150 mm、粒子径 5 μ m、資生堂、 Col. No. XXXXXXXXXX)
移動相	アセトニトリル/蒸留水混液 (8:2 v/v)
流速	1.0 mL/min
測定波長	230 nm
カラム設定温度	37°C
試料設定温度	25°C
測定時間	8 分
試料注入量	10 μ L
オートインジェクタ洗浄液	アセトニトリル
システム適合性	(1) 測定開始前にアセトンを用いて 1 回測定し、クロマトグラム上の <i>p</i> -サイメンの保持時間付近に妨害ピークがないことを確認した。 (2) 測定開始前および測定終了後に標準溶液 (St 2) を 1 回ずつ測定し、測定開始前に対する測定終了後の <i>p</i> -サイメンのピーク保持時間およびピーク面積の変動を確認した。変動の許容基準は、ピーク保持時間の差が ± 0.5 分以内、ピーク面積の偏差%が $\pm 5.0\%$ 以内を目安とした。

7) 数値の取り扱い

- (1) 標準原液および標準溶液の調製濃度は、切り捨てて有効数字 4 桁で表示した。
- (2) 投与検体の調製濃度は、四捨五入して有効数字 3 桁で表示した。
- (3) 試験結果における測定濃度および平均測定濃度は、切り捨てて有効数字 4 桁で表示した。
- (4) 含量 (%)、平均含量 (%) および相対標準偏差 (%) は、四捨五入して小数第 1 位まで表示した。
- (5) システム適合性におけるピーク保持時間およびピーク面積は、データ処理装置からの数値をそのまま使用した。ピーク保持時間の差 (分) およびピーク面積の偏差 (%) は、四捨五入して小数第 1 位まで表示した。
- (6) データ処理装置からの数値は、そのまま計算に使用した。