

平成 28 年度

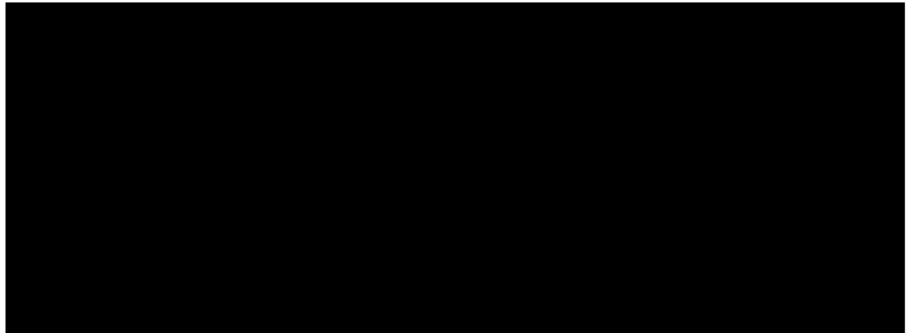
指定添加物の安全性に関する試験

2-butoxyethyl acetate 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 2-butoxyethyl acetate をトウモロコシ油に溶解して、0、20、100 および 500 mg/kg の用量で、各群とも雌雄各 10 匹の Cr1:CD (SD) ラットに 90 日間反復経口投与した。

その結果、一般状態の変化として 500 mg/kg 投与群の雌雄では、腹臥位および自発運動の低下が投与初日あるいは投与第 3 日に認められ、赤色尿が投与第 2 日に認められた。赤色尿は 100 mg/kg 投与群でも観察されたほか、投与後の一過性の流延が 100 および 500 mg/kg 投与群で認められた。

体重増加抑制が 500 mg/kg 投与群の雄で投与期間の後半に認められた。また、500 mg/kg 投与群の雌雄で投与第 1 日の摂餌量が低下した。

血液学的検査では、500 mg/kg 投与群の雌雄で赤血球数、血色素量、ヘマトクリット値、平均赤血球血色素濃度および好酸球比率の減少、平均赤血球容積、平均赤血球血色素量および網状赤血球比率の増加が認められた。また、500 mg/kg 投与群の雄では好中球比率の減少、リンパ球比率の増加が、雌では血小板数の減少およびプロトロンビン時間の延長が認められた。100 mg/kg 投与群の雌雄でも同様の貧血所見が認められた。

血液生化学的検査では、500 mg/kg 投与群の雌雄で無機リン濃度の増加がみられた。また、500 mg/kg 投与群の雄ではカリウムイオン濃度の増加、総コレステロール濃度、トリグリセライド濃度およびカルシウム濃度の減少が、雌ではアスパラギン酸アミノトランスフェラーゼ活性およびアラニンアミノトランスフェラーゼ活性の増加、総蛋白濃度、アルブミン濃度および総ビリルビン濃度の減少が認められた。100 mg/kg 投与群でも総ビリルビン濃度の減少、カリウムイオン濃度の増加が認められた。

病理学的検査では、500 mg/kg 投与群の雌雄で心臓、脾臓、肝臓および腎臓重量が増加し、100 mg/kg 投与群の雌でも肝臓重量が増加した。剖検所見では、脾臓は暗色化および大型化を呈し、病理組織学的検査では 100 および 500 mg/kg 投与群でヘモジデリン沈着の増加が、500 mg/kg 投与群では髄外造血の亢進が強く観察された。肝臓では、クッパー細胞のヘモジデリン沈着、小葉中心帯および小葉中間帯の肝細胞肥大が 100 および 500 mg/kg 投与群で、小肉芽腫の増加および門脈周囲性の肝細胞脂肪化の減少が 500 mg/kg 投与群で観察された。腎臓では、近位尿細管のヘモジデリン沈着が 100 および 500 mg/kg 投与群で、皮質の好塩基性尿細管および皮質または髄質の鉍質沈着の減少が 100 および 500 mg/kg 投与群で観察されたほか、大腿骨髄および胸骨髄の造血亢進が 100 および 500 mg/kg 投与群でみられた。その他、100 および 500 mg/kg 投与群の前胃粘膜に肥厚が観察された。

その他、500 mg/kg 投与群の雄 1 例が投与第 70 日に死亡したが、投与検体が逆流して誤嚥により死亡した可能性があり、同例以外に同様の変化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。また、雌雄ともに眼科学的検査および尿検査においては被験物質投与による影響は認められなかった。

以上の結果から、2-butoxyethyl acetate 投与による影響として、100 および 500 mg/kg 投与群で溶血性貧血、脾臓、肝臓および腎臓への影響がみられたことから、本試験条件下における 2-butoxyethyl acetate の無毒性量は、雌雄ともに 20 mg/kg/day と考えられた。

2. 試験目的

指定添加物である 2-butoxyethyl acetate の安全性に関する情報を得るために、ラットを用いる 90 日間反復経口投与毒性試験を実施した。

3. 試験ガイドラインと GLP

本試験は、「食品添加物の指定及び使用基準改正に関する指針」（平成 8 年 3 月 22 日 衛化第 29 号、以下、ガイドラインと略す）に準拠し、厚生省令第 21 号「医薬品の安全性に関する非臨床試験の実施の基準に関する省令」（平成 9 年 3 月 26 日、一部改正 厚生労働省令第 114 号 平成 20 年 6 月 13 日および厚生労働省令第 87 号 平成 26 年 7 月 30 日）を遵守して実施した。

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 [Crl: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 8 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。また、全例の眼科学的検査を行った。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：[REDACTED]

入荷時体重：雄 86.5~102.4 g (平均 95.3 g)、雌 66.1~77.7 g (平均 72.6 g)

検疫終了日：[REDACTED]

検疫終了時体重：雄 153.9~183.2 g (平均 168.8 g)、雌 103.4~138.7 g (平均 127.2 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。一方、眼科学的検査で水晶体後極のびまん性混濁が認められた雄 1 例 (馴化番号 M00017) および水晶体前極のびまん性混濁 (馴化番号 F00023)、水晶体後囊下の硝子体動脈遺残周囲の混濁 (馴化番号 F00027) および虹彩の後癒着 (馴化番号 F00043) が認められた雌 3 例は群分け対象から除外した。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 ([REDACTED]) の体重は平均体重の±20%以内であった [雄:160.8~191.3 g (平均 175.7 g)、雌:114.2~145.3 g (平均 131.8 g)]。試験に使用しなかった余剰動物の雌雄各 4 匹は剖検日 (雄 [REDACTED]、雌: [REDACTED]) にペントバルビタール麻酔下で腹部後大静脈より採血し、その後放血死により安楽死させた。

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 (220 w×270 d×190 h 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: [REDACTED]、日本クレア) および水道水 ([REDACTED] 水道局給水) 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 23.5~24.5°C、湿度の実測値は 42.5~63.0%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た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 [REDACTED] 号、第 [REDACTED] 号、第 [REDACTED] 号、第 [REDACTED] 号) および飼料分析試験成績書 ([REDACTED] 付、[REDACTED] 付、[REDACTED] 付、[REDACTED] 付) を、飲料水は水質検査結果書 ([REDACTED]) 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: [REDACTED]、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、媒体を加えて溶解させ 125 mg/mL 溶液を調製した。さらに 125 mg/mL 溶液を媒体によって希釈し、25 および 5 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: 23.5~24.5°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
BEA	20	5
BEA	100	25
BEA	500	125

2) 安定性試験

250 ならびに 2 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 () および投与期間中 () 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、初回投与検体の各平均含量は調製濃度の 100.9% (5.00 mg/mL)、98.9% (25.0 mg/mL)、96.3% (125 mg/mL) であり、各測定値のばらつきは平均値の 98.3~102.0%であった。投与期間中投与検体の各平均含量は 100.9% (5.00 mg/mL)、98.5% (25.0 mg/mL)、100.0% (125 mg/mL) であり、ばらつきは平均値の 98.0~101.2%であった。いずれも既定の範囲内であった (Annex 2)。

4) 投与検体中の被験物質濃度測定法

Annex 3 に従った。

5.4 投与量の設定および投与方法

投与量は、「2-butoxyethyl acetate 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 GLP 適用外) 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、1000 mg/kg 投与群の雌雄において、投与開始日から投与後第 4 日までに腹臥位および赤色尿が認められ、投与初期に摂餌量が減少した。血液学的検査では赤血球数および血色素量の減少、網状赤血球比率の上昇、好酸球比率の低下が 1000 mg/kg 投与群の雌雄で認められた。赤色尿および赤血球数の減少は 300 mg/kg 投与群の雌でも認められた。血液生化学検査では、ALT 活性の上昇が 300 および 1000 mg/kg 投与群の雌でみられ、肝臓の絶対重量および相対重量の増加が 1000 mg/kg の雌雄で、肝臓の相対重量の増加が 300 mg/kg の雌で認められた。また、1000 mg/kg 投与群では脾臓および腎臓の絶対重量および相対重量も増加した。

以上の結果から、2-butoxyethyl acetate 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、1000 mg/kg の半量である 500 mg/kg を高用量とし、以下公比 5 で、100 mg/kg を中用量、20 mg/kg を低用量に設定した。

投与経路は、ヒトが被験物質に暴露される可能性が最も高い経口投与とした。被験物質が液体であることから混餌検体作製において被験物質の均一性が得られない可能性があること、水に不溶であることから飲水投与が困難であること、さらに被験物質が香料であるため、対照群への暴露が懸念されることから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、9:00~10:49 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	BEA	20	4	5	M02011~M02020	F02051~F02060
中用量群	BEA	100	4	25	M03021~M03030	F03061~F03070
高用量群	BEA	500	4	125	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) および投与第 2 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 18~23 時間絶食) ならびに死亡時にも体重を測定した。なお、死亡動物の搬出時体重は本文中に記載し、帳票には記載しなかった。

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 週に雌雄とも対照群、中用量群および高用量群の全例（死亡例を除く）を検査した。対照群および高用量群の検査の結果、眼底の反射性亢進が高用量群の雄 2 例、雌 1 例で観察され、加齢性の自然発生性の所見と考えられたが、確認のため中用量群の検査を行った。その結果、眼底の反射性亢進が雄 1 例のみに観察されたが、少数例での変化であることから、加齢性の自然発生性の所見と判断し、低用量群の検査は実施しなかった。検査は肉眼的観察の後、双眼倒像鏡（バンテージ双眼倒像鏡 VA-2500 型、キーラー）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収容し、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、代謝ケージに収容後約 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。

動物番号 M03021、F02051、F02052 および F02053 のカリウムイオン濃度が範囲上限外であったため、尿試料を蒸留水で希釈して再測定を実施した。また、動物番号 F04072 の塩素イオン濃度が範囲下限外であったため、尿用標準液と尿試料を混合して再測定を実施した。

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 18～23 時間絶食させた。その後、ペントバルビタールナトリウム麻酔下で、腹部後大静脈より下記 (1)～(4) の順序で採血した。また、採血は可能な限り、雌雄ともに対照群、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

項目	測定法	使用機器
血色素量 (HGB)	SLS ヘモグロビン法	血液自動分析装置 XT-2000iV (シスメックス)
血小板数 (PLT)	電気抵抗検出法	同上
ヘマトクリット値 (HCT)	同上	同上
平均赤血球容積 (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の有意な減少が 500 mg/kg 投与群の雌で認められたが、総蛋白濃度の減少はアルブミン濃度の減少に起因した変化と考えられた。また、A/G 比の有意な上昇が 500 mg/kg 投与群の雄で認められたが、総蛋白濃度に変動はみられなかった。以上のことから、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・ HMPS 法	同上
トリグリセライド濃度 (TG)	GPO・HMPS 法、グリセリン消去 法	同上
総ビリルビン濃度 (tbil)	酵素法	同上
尿素窒素濃度 (BUN)	ウレアーゼ・G α LDH 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・HMPS 法	同上
クレアチン・フォスフォキナーゼ濃 度 (CPK)	JSCC 標準化対応法	同上
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)	IFCC 法	同上
アルカリフォスファターゼ活性 (ALP)	GSCC 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
無機リン濃度 (IP)	モリブデン酸直接法	同上
カルシウム濃度 (Ca)	OCPC 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

死亡例以外の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、全身の器官・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。死亡例は速やかに剖検し、器官・組織の肉眼的観察を実施した。

重量測定器官名：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

死亡例（動物番号 M04036）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は、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。検査の結果、肝臓、腎臓、脾臓および骨髓（大腿骨・胸骨）の高用量群において、被験物質投与による変化が疑われたため、当該器官の低および中用量群の病理組織学的検査を実施した。また、剖検時、被験物質投与群において肉眼的な変化が散見された胃についても低および中用量群の病理組織学的検査を実施した。

鏡検時、肝臓、腎臓および脾臓に褐色色素沈着が認められたため、褐色色素の鑑別のため代表例（動物番号 M01001、M02012、M03023、M04034、F01041、F02054、F03068、F04073）についてベルリン青染色を実施した。その結果、各臓器の沈着部位が陽性であったことから所見名をヘモジデリン沈着とした。

なお、雄1例（動物番号 M01003）の右側副腎については、剖検時に小型化がみられたが、鏡検観察により明らかに副腎組織ではなかったため当該剖検所見を削除した。これに伴い、器官重量データにおいて、同例の副腎は右側重量を削除し、左側重量を参考データとした。

固定器官・組織名：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、膾、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樣性について検定を行った。分散が一樣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、Dunnett法により多重比較を行った。一方、分散が一樣でなかった場合は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Dunnett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っ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ったこと

血液自動分析装置（XT-2000iV）を用いる血液検査の標準操作手順書では、直線性限界外の測定値の場合、確認用の再測定を1回行う旨記載されているが、直線性限界外の測定値となった高用量群の雄1例（動物番号 M04034）の網状赤血球比率において確認用の再測定を行わなかった。高

用量群では被験物質投与による網状赤血球比率の上昇がみられており、高用量群の雌でも直線性限界外の測定値を示した動物があり、再測定を実施し、同様の測定値が得られている。このことから、動物番号 M04034 でも網状赤血球比率が増加していたと考えられ、再測定による確認は行っていないが同測定値を採用する事に問題はないと判断した。よって、本逸脱による試験への影響はないと判断した。

その他、本試験期間中に「予見することができなかっ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ったこと」はなかった。

7. 試験成績

7.1 一般状態 (Table 1, Appendix 1)

500 mg/kg 投与群では、腹臥位および自発運動の低下が投与初日あるいは投与第 3 日の投与後に雌雄各 1~3 例で認められたほか、赤色尿が投与第 2 日の投与前に雌雄各 4 例で認められた。腹臥位は投与第 18 日にも雄 1 例で認められた。また、投与後の一過性の流涎が投与第 3 日から投与期間を通して断続的に雌雄で認められた。その他、軟便が投与第 3 日に雌 1 例で、給餌器からの餌こぼしが投与第 79~88 日に雄 2 例および雌 1 例で認められた。

100 mg/kg 投与群では、赤色尿が雄 1 例 (投与第 59 日投与前) および雌 1 例 (投与第 87 日投与前) で、投与後の流涎が投与第 81 および 84 日に雄 1 例で認められた。

20 mg/kg 投与群では、雄 1 例 (動物番号 M02014) で投与第 57 日から切歯の欠損が認められ、投与第 64 日に回復した。これは物理的な欠損と考えられ、被験物質投与との関連はないと考えられた。その他、一般状態の異常は観察されなかった。

500 mg/kg 投与群の雄 1 例 (動物番号 M04036) では投与第 68 日の投与後に自発運動の低下および流涎が認められ、以降も症状は継続し、投与第 70 日に腹臥位、半眼、鼻周囲汚れおよび排便量減少が認められ、同日の投与後に死亡した。その他、いずれの群においても、観察期間中に死亡例はなかった。

7.2 体重 (Table 2, Appendix 2)

500 mg/kg 投与群の雄の体重が投与期間の後半に対照群と比較して低い傾向がみられた。しかし、雌雄ともに対照群と各被験物質投与群との間の体重に有意な差は認められなかった。

投与第 57 日の測定で、切歯の欠損が認められた 20 mg/kg 投与群の雄 1 例 (動物番号 M02014) の体重が減少したが、投与第 64 日の測定日以降の体重は増加した。

投与第 70 日に死亡した 500 mg/kg 投与群の雄 1 例 (動物番号 M04036) の体重は投与第 64 日まで順調に増加し、投与第 64 日の体重は 515.2 g であったが、死亡時体重 (投与第 70 日) は 397.0 g と減少した。

7.3 摂餌量 (Table 3, Appendix 3)

500 mg/kg 投与群の雌雄で投与第 1 日の摂餌量が対照群と比較して有意に低下した。また、500 mg/kg 投与群の雄では投与第 64 日、同群の雌では投与第 29 日から第 85 日の各測定日の摂餌量が対照群と比較して有意に高値を示した。

20 および 100 mg/kg の摂餌量は対照群と比較して有意な差は認められなかった。

7.4 眼科学的検査 (Table 4, Appendix 4)

投与第 12 週の検査では、帯状の眼底反射性亢進が 500 mg/kg 投与群の雄 2 例、雌 1 例、100 mg/kg 投与群の雄 1 例に認められた。対照群の雄 1 例には眼底に散在性の点状の褐色斑が認められた。その他、対照群、100 および 500 mg/kg 投与群の雌雄で帯状の角膜混濁が、100 mg/kg 投与群の雄で硝子体動脈遺残が観察されたが、1 例を除きいずれも検疫期間中から認められた所見であった。

7.5 尿検査 (Table 5, Appendix 5)

500 mg/kg 投与群の雌の尿量が対照群と比較して有意に増加した。個体別にみると、尿量が多い動物では比重および尿中電解質濃度が低値を示した。その他、雌雄とも各検査項目に変化はな

く、尿量、比重および尿中電解質においても対照群と各被験物質投与群との間に有意な差は認められなかった。

7.6 血液学的検査 (Table 6, Appendix 6)

500 mg/kg 投与群の雌雄で赤血球数、血色素量、ヘマトクリット値、平均赤血球血色素濃度および好酸球比率の有意な減少、平均赤血球容積、平均赤血球血色素量および網状赤血球比率の有意な増加が認められた。また、500 mg/kg 投与群の雄では好中球比率の有意な減少、リンパ球比率の有意な増加およびプロトロンビン時間の有意な短縮が、雌では血小板数の有意な減少およびプロトロンビン時間の有意な延長が認められた。

100 mg/kg 投与群の雌雄では赤血球数および血色素量の有意な減少が認められ、さらに雌ではヘマトクリット値および平均赤血球血色素濃度の有意な減少、平均赤血球容積、平均赤血球血色素量および網状赤血球比率の有意な増加が認められた。

20 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)

500 mg/kg 投与群の雌雄で無機リン濃度の有意な増加がみられた。また、500 mg/kg 投与群の雄では A/G 比およびカリウムイオン濃度の有意な増加、総コレステロール濃度、トリグリセライド濃度およびカルシウム濃度の有意な減少が認められ、雌ではアスパラギン酸アミノトランスフェラーゼ活性およびアラニンアミノトランスフェラーゼ活性の有意な増加、総蛋白濃度、アルブミン濃度および総ビリルビン濃度の有意な減少が認められた。

100 mg/kg 投与群の雌雄では、総ビリルビン濃度が有意に減少し、雄ではカリウムイオン濃度が有意に増加した。

20 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)

500 mg/kg 投与群の雄では、解剖時体重が有意に減少し、脾臓の実重量および相対重量が有意に増加した。また、脳、心臓、肝臓、腎臓（左右および合計値）の相対重量が有意に増加した。顎下腺は実重量が有意に減少した。500 mg/kg 投与群の雌では、肝臓、腎臓（左右および合計値）、脾臓の実重量および相対重量が有意に増加した。また、心臓の相対重量が有意に増加した。

100 mg/kg 投与群では、雌の肝臓の実重量および相対重量が有意に増加した。

20 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。

7.9 剖検所見 (Table 9, Appendix 9)

500 mg/kg 投与群の雌雄の生存例全例および 100 mg/kg 投与群の雄 2 例では脾臓の暗色化がみられ、その内 500 mg/kg 投与群の雄 8 例および雌 9 例では大型化を伴っていた。また、500 mg/kg 投与群の雄 7 例および雌 4 例ならびに 100 mg/kg 投与群の雄 1 例では前胃粘膜に肥厚が認められた。その他、500 mg/kg 投与群において胸腺の小型化および左側腎臓に淡色斑が雄各 1 例に、回腸に憩室が雄 2 例にみられ、100 mg/kg 投与群では脳に限局性の陥凹および頭蓋骨の頭蓋腔側に限局性の隆起が雄 1 例に認められた。20 mg/kg 投与群では雌雄とも異常所見は認められなかった。

投与第 70 日に死亡した 500 mg/kg 投与群の雄 1 例では、肺の暗赤色化、心臓に散在性の白色斑、脾臓の小型化および淡色化、胃の腺胃粘膜に黒色付着物および前胃粘膜に隆起部、胸腺の小型化がみられたほか、盲腸の内容物減少、食道内腔の拡張および泡沫液貯留、口周囲および眼周囲に被毛の汚れが認められた。

7.10 病理組織学的検査所見 (Table 10, Appendix 10)

7.10.1 定期解剖例

被験物質投与との関連がある変化として、脾臓のうっ血が雌の 500 mg/kg 投与群の 1 例で認められた。肝臓では、クッパー細胞のヘモジデリン沈着 (Photo 1, Photo 2, Photo 7) が雄の 500 mg/kg 投与群の全例、100 mg/kg 投与群の 2 例に、雌の 500 mg/kg 投与群の全例、100 mg/kg 投与群の 5 例に観察された。その内、雌雄の 500 mg/kg 投与群では対照群と比較して発生頻度および

変化の程度ともに有意な増強が、雌の 100 mg/kg 投与群では発生頻度の増加が認められた。また、小葉中心帯および小葉中間帯の肝細胞肥大が雄の 500 mg/kg 投与群の 5 例に、雌の 500 mg/kg 投与群の全例、100 mg/kg 投与群の 3 例に観察された。その内、雌雄の 500 mg/kg 投与群において対照群と比較し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。肝臓の髄外造血が雌の 500 mg/kg 投与群の 1 例に認められた。腎臓では、近位尿細管のヘモジデリン沈着 (Photo 8) が雌雄の 500 mg/kg 投与群の全例に、雌の 100 mg/kg 投与群の 3 例に観察された。その内、雌雄の 500 mg/kg 投与群において対照群と比較し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。大腿骨骨髄では、造血亢進 (Photo 3、Photo 4) が 500 mg/kg 投与群の雌雄全例に、100 mg/kg 投与群の雄 2 例および雌 3 例に観察され、雌雄の 500 mg/kg 投与群において対照群と比較し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。胸骨骨髄では、造血亢進が 500 mg/kg 投与群の雌雄全例に、100 mg/kg 投与群の雌雄各 1 例に観察され、雌雄の 500 mg/kg 投与群において対照群と比較して発生頻度および程度ともに有意な増強が認められた。胃では、境界縁上皮層の空胞化が雄の 500 mg/kg 投与群の 1 例に観察された。

対照群にも散見されたが、対照群と比較して発生頻度あるいは変化の程度に有意差が認められた変化として、脾臓では、ヘモジデリン沈着 (Photo 5、Photo 6、Photo 9) が全群全例に観察され、その内、雄では 500 および 100 mg/kg 投与群に、雌では 500 mg/kg 投与群において対照群と比較して変化の程度が有意に強かった。また、脾臓の髄外造血が全群全例に観察され、その内、雌雄ともに 500 mg/kg 投与群において対照群と比較して変化の程度が有意に強かった。肝臓では、小肉芽腫が雄の 500 mg/kg 投与群の 3 例、100 mg/kg 投与群および対照群の各 4 例、20 mg/kg 投与群の 2 例に、雌の 500 mg/kg 投与群の 7 例、100 mg/kg 投与群の 5 例、20 mg/kg 投与群の 3 例、対照群の 2 例に観察された。その内、雌の 500 mg/kg 投与群において対照群と比較して発生頻度の有意な増加が認められた。一方、門脈周囲性の肝細胞の脂肪化が雄の 500 mg/kg 投与群の 4 例、100 mg/kg 投与群の 9 例、20 mg/kg 投与群および対照群の全例に、雌の 500 mg/kg 投与群の 7 例、100 mg/kg 投与群の 8 例、20 mg/kg 投与群および対照群の各 5 例に観察された。その内、雄の 500 mg/kg 投与群において対照群と比較して発生頻度および変化の程度ともに有意な減弱が認められた。腎臓では、皮質の好塩基性尿細管が雄の 100 mg/kg 投与群の 2 例、20 mg/kg 投与群の 5 例、対照群の 4 例に、雌の 100 mg/kg 投与群の 2 例、20 mg/kg 投与群の 3 例、対照群の 4 例に観察され、その内、雌の 500 mg/kg 投与群において対照群と比較して発生頻度の有意な減少が認められた。また、皮質または髄質の鉍質沈着が雄の 500 mg/kg 投与群 1 例、100 mg/kg および 20 mg/kg 投与群の各 2 例、対照群の 3 例に、雌の 500 mg/kg 投与群の 1 例、100 mg/kg 投与群の 2 例、20 mg/kg 投与群の 6 例、対照群の 7 例に観察された。その内、雌では 500 mg/kg 投与群において対照群と比較して発生頻度および変化の程度ともに有意な減弱が、100 mg/kg 投与群では発生頻度の減少が認められた。胃では、境界縁の固有層に水腫が雄の 500 mg/kg 投与群の 6 例、100 mg/kg 投与群および対照群の各 3 例、20 mg/kg 投与群の 4 例に、雌の被験物質投与群の各 4 例、対照群の 2 例に観察された。その内、雄の 500 mg/kg 投与群において有意な差はないものの、対照群と比較して発生頻度および変化の程度が増強する傾向が認められた。

対照群にも散見された変化として、肝臓での Tension lipidosis が雄の 500 mg/kg 投与群の 2 例ならびに雌の 100 mg/kg 投与群および対照群の各 1 例に観察された。腎臓では、間質のリンパ球浸潤が雄の 500 mg/kg 投与群、20 mg/kg 投与群および対照群の各 1 例に、雌の 100 および 20 mg/kg 投与群の各 1 例、対照群の 3 例に、皮質または髄質の嚢胞が雌の 20 mg/kg 投与群および対照群の各 1 例に、炎症細胞浸潤を伴う腎盂の移行上皮過形成が雌の 20 mg/kg 投与群および対照群の各 1 例に、皮質の限局性尿細管内出血が雄の対照群の 1 例に観察された。その他、雌雄のハーダー腺、鼻腔、甲状腺、胸腺、心臓および肺に、雄の下垂体、眼球、ジンバル腺、膵臓および前立腺に所見が認められた。これらの所見はいずれも対照群と比較して発生頻度および変化の程度ともに有意差は認められなかったことから、偶発性的変化と判断した。

また、剖検所見がみられた器官において、雄の 500 mg/kg 投与群 1 例の胸腺では萎縮がみられたが、変化の程度は軽微であった。雄の 500 mg/kg 投与群 2 例の回腸では、憩室がみられたが組織学的な異常は認められなかった。雄の 100 mg/kg 投与群 1 例の脳では髄膜の肥厚、単核細胞浸潤および褐色色素沈着がいずれも限局性にみられ、同例の頭蓋骨では限局性の肥厚が認められた。その他、500 mg/kg 投与群では、雄の副腎および精巣上体に、雌の顎下腺、舌下腺および卵巣に

所見が認められたが、いずれの所見も少数例のみの変化で、軽微あるいは軽度な変化であったことから、自然発生的あるいは先天的な変化と判断した。

7.10.2 死亡例

肺では肺泡に顕著な水腫が、気管支周囲および内腔に好中球またはマクロファージ浸潤が軽度に見られた。さらに、心臓では血管周囲に鉍質沈着を伴った多巣性の心筋の変性/壊死が中等度にみられたほか、動脈壁の鉍質沈着および限局性の心筋の線維化が軽度に、単核細胞浸潤が軽微に認められた。胸腺、脾臓および顎下リンパ節では、軽度から著しい萎縮が観察され、その内、顎下リンパ節ではリンパ球のびまん性壊死を伴っていた。また、骨髄（大腿骨および胸骨）では、造血低下およびマクロファージ浸潤が観察され、その内、大腿骨骨髄では壊死も認められた。

ヘモジデリン沈着は、生存例と同様に脾臓および肝臓に認められた。

剖検所見がみられたその他の器官において、胃では前胃粘膜に潰瘍が観察された。

その他、鼻腔、甲状腺、副腎、精巣上体に所見が認められた。なお、空腸では、自己融解が顕著であったため組織学的な評価ができなかった。

8. 考察

指定添加物である 2-butoxyethyl acetate をトウモロコシ油に溶解して、0、20、100 および 500 mg/kg の用量で、各群とも雌雄各 10 匹の Cr1:CD (SD) ラットに 90 日間反復経口投与した。

被験物質投与による一般状態の変化として、赤色尿が 500 mg/kg 投与群で投与第 2 日のみに、100 mg/kg 投与群で投与期間の後半に 1 日のみ観察された。後述するように赤色尿は溶血性貧血に伴う血色素尿であると考えられた。また、500 mg/kg 投与群では、投与初日あるいは投与第 3 日に腹臥位および自発運動の低下が認められ、投与第 1~2 日の摂餌量が減少した。さらに、100 および 500 mg/kg 投与群では投与後の一過性の流涎が認められ、剖検で 100 および 500 mg/kg 投与群の前胃粘膜に肥厚が観察され、被験物質の刺激性による変化と考えられた。なお、500 mg/kg 投与群では投与第 29 日以降の摂餌量が高値を示したが、体重に有意な増加は認められず、一般状態観察で餌こぼしが散見されているため、被験物質の刺激性が、摂餌行動を促した可能性が考えられた。

500 mg/kg 投与群の雄では、体重増加抑制が投与期間の後半に認められ、被験物質投与による影響と考えられた。

血液学的検査では、100 および 500 mg/kg 投与群で赤血球数、血色素量、ヘマトクリット値、平均赤血球血色素濃度の減少、平均赤血球容積、平均赤血球血色素量および網状赤血球比率の増加が認められた。病理組織学的検査では、100 および 500 mg/kg 投与群の大腿骨および胸骨骨髄に造血亢進が認められたことから、被験物質投与により貧血が生じることが明らかとなった。一般状態の観察では赤色尿が認められ、脾臓、肝臓および腎臓重量が増加し、脾臓は暗色化および大型化を呈し、病理組織学的検査では 100 および 500 mg/kg 投与群でヘモジデリン沈着が、500 mg/kg 投与群では髄外造血が強く観察された。ヘモジデリン沈着は肝臓のクッパー細胞および腎臓の近位尿細管でも観察された。しかし、血中 CPK 活性に変動はなく、筋肉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、本試験でみられた赤色尿はミオグロビン尿ではなく血色素尿であり、溶血性貧血が生じていることが明らかとなった。溶血性貧血に伴う変化として、脾臓機能亢進によると考えられる血小板数の減少が 500 mg/kg 投与群の雌で認められた。血液生化学的検査でみられたカリウムイオン濃度の増加は溶血により赤血球内のカリウムイオンが流出したためと考えられた。また、総ビリルビン濃度が減少した。一般的に溶血性貧血があると血中ビリルビン量が増加するが、長期にわたる高度の貧血のためヘモグロビン代謝が低下し、ビリルビン量が減少した可能性が考えられた。さらに、500 mg/kg 投与群の心臓の相対重量が増加し、病理組織学的に心筋肥大はみられなかったが、長期にわたる貧血のために代償性の心臓肥大が生じている可能性も考えられた。

前述した以外の血液学的検査では、500 mg/kg 投与群の雄で好酸球および好中球比率の減少、リンパ球比率の増加が認められ、同群の雌でも好酸球比率が減少した。「2-butoxyethyl acetate 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 ██████████) でも好酸球比率の低下が 1000 mg/kg 投与群で認められていることから、好酸球比率の低下は被験物質投

与による影響と考えられた。また、500 mg/kg 投与群の雌ではプロトロンビン時間の延長が認められ、血液生化学的検査では、同群の雄で総コレステロールおよびトリグリセライド濃度の減少が、同群の雌で総蛋白およびアルブミン濃度の減少、アスパラギン酸アミノトランスフェラーゼ活性およびアラニンアミノトランスフェラーゼ活性の増加がみられた。病理学的変化として、肝臓重量が増加し、小葉中心帯および小葉中間帯の肝細胞肥大および小肉芽腫の増加がみられたほか、門脈周囲性の肝細胞の脂肪化の減少が観察されていることから、被験物質投与による肝機能障害で血液凝固因子、蛋白合成や脂質代謝の低下が生じていると考えられた。なお、プロトロンビン時間の短縮が500 mg/kg 投与群の雄でみられたが、プロトロンビン時間の短縮の毒性学的意義は低いと、偶発的変化と考えられた。

血液生化学的検査では、前述した変化以外に500 mg/kg 投与群の雌雄で無機リン濃度が増加し、同群の雄ではカルシウム濃度の減少がみられた。病理学的変化として、腎臓重量が増加しており、予備試験（試験番号 ████████）でも腎臓重量の増加が1000 mg/kg 投与群で認められていることから、腎機能障害による血中の無機リン増加およびカルシウム減少の可能性が考えられた。しかし、尿素窒素やクレアチニン濃度の増加など腎障害を示唆する所見は認められなかった。また、腎臓での皮質の好塩基性尿細管および皮質または髄質の鉍質沈着の減少が100あるいは500 mg/kg 投与群でみられたが、その発生機序については明らかにできなかった。その他、500 mg/kg 投与群の雄ではA/G比が増加したが、総蛋白濃度およびアルブミン濃度に変動はなく、被験物質投与との関連はないと考えられた。

器官重量の測定では、前述した心臓、脾臓、肝臓および腎臓重量の増加のほか、500 mg/kg 投与群の脳相対重量が増加したが、病理組織学的な異常は認められなかったことから、解剖時体重が低値であったことによる影響と考えられた。また、500 mg/kg 投与群の雄で顎下腺の実重量が減少したが、病理組織学的な異常は認められなかったことから被験物質投与の影響ではないと判断した。

500 mg/kg 投与群の雄1例が投与第70日に死亡した。同例では、投与第68日の投与後から自発運動の低下および流涎が認められ、第70日に半眼、鼻周囲汚れ、排便量減少などが観察され状態が急変し、投与後に死亡した。剖検の結果、肺の暗赤色化、心臓に散在性の白色斑が観察され、病理組織学的検査では肺では肺泡に顕著な水腫、心臓の血管周囲に鉍質沈着を伴った多巣性の心筋の変性/壊死が認められた。また、胃の腺胃粘膜に黒色付着物および前胃粘膜に隆起部、盲腸の内容物減少、食道の内腔が拡張し泡沫液貯留などが認められた。ゾンデによる食道穿孔は認められず、急激に状態が悪化したことから、投与検体が食道から逆流して誤嚥を起こした可能性が考えられた。同例以外に同様の変化は認められなかったことから、死亡と被験物質投与との関連はないと判断した。

その他、投与第12週の眼科学的検査では、眼底の反射性亢進が100および500 mg/kg 投与群で散見されたが、少数例での変化であることから、加齢性の自然発生性所見と判断した¹⁾。尿検査では、500 mg/kg 投与群の雌で尿量が増加したが、尿中電解質排泄量に変化はないため、被験物質投与の影響ではないと考えられた。

以上の結果から、2-butoxyethyl acetate 投与による影響として、100および500 mg/kg 投与群で溶血性貧血、脾臓、肝臓および腎臓への影響がみられたことから、本試験条件下における2-butoxyethyl acetate の無毒性量は、雌雄ともに20 mg/kg/day と考えられた。

9. 参考文献

- 1) 奥春孝、日比大介、黒田顕：Cr1:CD (SD) 系ラットの26週間飼育における自然発生性眼病変の経時的推移。比較眼科研究 35: 35-41 (2016)

Table 1 (Continued)
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 General condition of males

Group	Number of males and general conditions	Days of administration																																																	
		51		52		53		54		55		56		57		58		59		60		61		62		63		64		65		66		67		68		69		70		71		72		73		74		75	
		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	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	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	10	10	10	10	10	
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 20 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	10	10	10	10	10	10	10	10	10	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Medium dose (BEA 100 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	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	9	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Excretion, Reddish urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 500 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	10	10	10	10	10	10	10			
	General appearance, No abnormality	10	8	10	7	10	8	10	9	10	8	10	9	10	9	10	8	10	7	10	6	10	8	10	6	10	8	10	6	10	8	10	8	10	8	10	8	9	8	9	7	9	8	9	7	9	7	9	7	9	
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0		
	Mouth, Salivation	0	2	0	3	0	2	0	1	0	2	0	1	0	1	0	2	0	3	0	4	0	2	0	4	0	2	0	4	0	2	0	2	0	2	0	2	0	2	1	2	1	3	0	1						

Table 1 (Continued)
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 General condition of females

Group	Number of females and general conditions	Days of administration																																																			
		51		52		53		54		55		56		57		58		59		60		61		62		63		64		65		66		67		68		69		70		71		72		73		74		75			
		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	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	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	10	10	10	10	10	10	10	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 20 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	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	10	10	10	10	10	10	10	
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Medium dose (BEA 100 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	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	10	10	10	10	10	10	10	10
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 500 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	10	10	10	10	10	10	10	10	
	General appearance, No abnormality	10	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	9	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Mouth, Salivation	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

Pre: Before administration, Post: after administration.

Group	Number of females and general conditions	Days of administration																																																		
		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							
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	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	10	10	10	10			
	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	0	0	0	0	0	0	0	0	0			
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 20 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	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	10	10	10	10	10		
	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	0	0	0	0	0	0	0	0	0	0		
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Medium dose (BEA 100 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	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	10	10	10	10	10	10	
	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	0	0	0	0	0	0	0	0	0	0	0	0
	Mouth, Salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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 (BEA 500 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	10	10	10	10	10	10		
	General appearance, No abnormality	10	10	10	9	10	10	10	10	10	10	10	10	9	10	10	10	10	9	10	9	10	9	10	9	10	9	10	9	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	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	0	0	0	0	0	0	0	0	0	0	0	
	Mouth, Salivation	0	0	0	1	0	1	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	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 2-butoxyethyl acetate in rats
 Body weight of males

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of males	10	10	10	10
Days of administration				
1	177.1 ± 7.8	175.6 ± 7.9	174.8 ± 6.9	175.3 ± 8.7
2	183.6 ± 8.2	183.7 ± 9.5	182.9 ± 8.0	179.2 ± 9.6
8	236.4 ± 13.5	235.5 ± 15.2	232.2 ± 14.4	230.4 ± 13.4
15	298.6 ± 20.7	297.9 ± 21.1	292.8 ± 22.6	289.4 ± 14.7
22	355.7 ± 26.3	355.4 ± 28.3	347.9 ± 30.1	341.6 ± 16.7
29	402.7 ± 33.6	400.7 ± 35.8	391.2 ± 40.0	381.4 ± 18.7
36	443.2 ± 35.3	442.5 ± 42.5	428.6 ± 47.6	414.2 ± 16.8
43	479.7 ± 37.7	475.2 ± 48.3	459.6 ± 54.7	445.5 ± 19.0
50	510.6 ± 43.0	503.4 ± 51.5	487.2 ± 56.3	470.7 ± 22.3
57	535.3 ± 46.4	520.1 ± 51.5	512.7 ± 59.7	490.0 ± 24.8
64	558.5 ± 50.2	539.3 ± 52.4	530.2 ± 58.6	507.8 ± 29.4
71	581.9 ± 54.4	559.5 ± 57.2	552.0 ± 61.9	524.6 ± 31.1 (9)
78	602.7 ± 56.5	579.3 ± 57.6	571.5 ± 63.5	539.2 ± 32.4 (9)
85	614.9 ± 59.7	595.2 ± 59.6	583.4 ± 64.8	548.7 ± 31.8 (9)
90	623.4 ± 62.4	603.0 ± 58.5	591.0 ± 64.3	552.9 ± 32.6 (9)

Each value shows mean (g) ± S.D.

Figures in parentheses indicate number of males.

Table 2 (Continued)
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Body weight of females

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of females	10	10	10	10
Days of administration				
1	131.6 ± 6.0	130.5 ± 8.0	131.1 ± 8.2	133.8 ± 6.8
2	137.0 ± 7.0	135.0 ± 7.8	134.7 ± 9.8	135.2 ± 8.4
8	161.3 ± 10.6	158.5 ± 8.0	159.7 ± 13.8	161.1 ± 10.5
15	178.7 ± 15.9	179.1 ± 10.5	181.2 ± 18.4	181.4 ± 12.1
22	198.3 ± 19.8	198.8 ± 12.6	201.6 ± 19.1	207.1 ± 14.6
29	215.9 ± 22.4	221.2 ± 15.2	219.2 ± 22.6	227.2 ± 12.5
36	228.0 ± 22.1	237.0 ± 18.9	232.4 ± 26.5	244.3 ± 17.3
43	238.7 ± 28.7	247.4 ± 21.7	244.2 ± 26.9	255.0 ± 18.7
50	250.3 ± 28.2	259.9 ± 22.0	256.4 ± 26.5	267.3 ± 19.4
57	261.8 ± 28.9	270.6 ± 25.2	264.1 ± 24.2	274.1 ± 15.1
64	269.2 ± 31.7	278.5 ± 28.2	273.3 ± 31.6	281.2 ± 18.8
71	275.9 ± 29.1	286.5 ± 31.4	283.6 ± 33.0	288.6 ± 22.1
78	284.4 ± 27.2	292.6 ± 31.3	291.5 ± 30.6	296.3 ± 18.9
85	286.0 ± 27.9	300.4 ± 33.2	294.6 ± 30.2	299.7 ± 19.9
91	288.9 ± 28.9	302.1 ± 35.4	295.8 ± 32.2	300.2 ± 21.0

Each value shows mean (g) ± S.D.

Table 3

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Food consumption of males

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of males	10	10	10	10
Days of administration				
1	22.6 ± 1.7	23.0 ± 2.6	21.7 ± 1.9	18.0 ± 2.2 **
8	24.4 ± 2.5	24.0 ± 2.0	23.5 ± 2.7	23.6 ± 2.8
15	25.7 ± 3.2	25.1 ± 1.4	24.3 ± 2.0	25.8 ± 3.0
22	26.4 ± 3.9	25.8 ± 2.7	25.6 ± 2.9	25.7 ± 3.1
29	25.9 ± 1.1	25.9 ± 2.8	26.3 ± 3.4	27.5 ± 2.7
36	26.4 ± 2.0	26.3 ± 3.0	25.2 ± 2.9	26.2 ± 3.7
43	25.3 ± 2.9	25.5 ± 2.7	25.3 ± 2.9	25.7 ± 2.7
50	25.8 ± 2.8	23.4 ± 2.5	23.8 ± 2.7	26.6 ± 3.4
57	26.1 ± 2.6	23.9 ± 1.7	24.1 ± 2.6	27.7 ± 2.4
64	25.1 ± 2.4	23.8 ± 3.3	24.6 ± 2.6	28.2 ± 2.4 *
71	24.9 ± 3.2	24.1 ± 3.6	24.3 ± 2.1	25.5 ± 2.5 (9)
78	23.2 ± 3.0	21.4 ± 2.9	22.6 ± 1.7	27.0 ± 5.2 (9)
85	22.3 ± 4.1	22.6 ± 3.1	21.7 ± 1.9	24.4 ± 2.3 (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 males.

Table 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of females

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of females	10	10	10	10
Days of administration				
1	18.1 ± 1.5	16.8 ± 1.4	16.0 ± 1.8	15.0 ± 2.8 **
8	16.0 ± 1.6	15.9 ± 1.6	16.5 ± 2.1	16.8 ± 0.9
15	15.9 ± 1.7	17.0 ± 1.9	16.7 ± 1.5	18.0 ± 1.6
22	16.3 ± 2.4	16.1 ± 2.5	15.4 ± 2.5	18.7 ± 2.8
29	15.7 ± 2.9	16.8 ± 2.6	17.1 ± 1.6	21.7 ± 3.2 **
36	16.1 ± 1.8	16.8 ± 3.1	16.8 ± 2.0	19.2 ± 2.4 *
43	16.0 ± 1.7	16.5 ± 2.6	16.1 ± 3.0	21.0 ± 3.0 **
50	13.4 ± 2.5	15.2 ± 2.3	16.5 ± 2.4	19.5 ± 4.5 **
57	16.0 ± 2.3	15.4 ± 2.7	17.3 ± 1.7	21.2 ± 2.1 **
64	15.3 ± 1.8	15.7 ± 2.8	16.1 ± 2.0	21.0 ± 2.9 **
71	15.3 ± 2.2	15.2 ± 2.8	16.0 ± 2.6	22.1 ± 5.2 **
78	14.6 ± 3.2	14.3 ± 3.5	16.2 ± 2.5	19.3 ± 2.6 **
85	13.2 ± 1.7	14.8 ± 2.3	15.2 ± 2.1	18.2 ± 2.8 **

Each value shows mean (g) ± S.D.

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

Table 4
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Ophthalmologic examination

Males

Findings	Group	Control (vehicle: corn oil)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
	Grade	-	+	-	+	-	+
Cornea							
Band-shaped opacity		7	3	3	7	5	4
Vitreous							
Persistent hyaloid artery		10	0	7	3	9	0
Fundus							
Scattered brown spots area		9	1	10	0	9	0
Band-shaped hyper reflection		10	0	9	1	7	2

-, not observed

+, observed

Number represent the number of animals.

Females

Findings	Group	Control (vehicle: corn oil)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
	Grade	-	+	-	+	-	+
Cornea							
Band-shaped opacity		9	1	7	3	7	3
Fundus							
Band-shaped hyper reflection		10	0	10	0	9	1

-, not observed

+, observed

Number represent the number of animals.

Table 5
Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Urinalysis of males

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of males	5	5	5	5
pH				
6.5	1	1	2	1
7.0	1	1	0	0
7.5	0	0	2	3
8.0	1	3	0	1
8.5	1	0	1	0
≥9.0	1	0	0	0
Protein				
- (negative)	0	0	0	0
± (10 ≤ and < 30 mg/dL)	0	3	0	2
+ (30 ≤ and < 100 mg/dL)	2	1	2	3
2+ (100 ≤ and < 300 mg/dL)	3	1	3	0
Glucose				
- (negative)	5	5	5	5
Ketone				
- (negative)	0	2	1	2
± (5 ≤ and < 10 mg/dL)	2	2	1	3
+ (10 ≤ and < 40 mg/dL)	3	1	3	0
Bilirubin				
- (negative)	5	5	5	5
Occult blood				
- (negative)	5	5	5	5
Urobilinogen				
± (normal)	1	4	2	3
+ (2.0 ≤ and < 4.0 mg/dL)	2	1	2	2
2+ (4.0 ≤ and < 8.0 mg/dL)	2	0	1	0
Color				
light yellow	4	5	5	5
yellow	1	0	0	0
Turbidity				
- (negative)	5	5	3	5
± (trace)	0	0	0	0
+ (slight)	0	0	2	0
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
Cristals				
- (not observed)	0	3	0	0
± (a few)	5	2	5	5
Epithelial cells				
- (not observed)	5	5	5	4
± (a few)	0	0	0	1

Table 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of males

Group	Control (vehicle: corn oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
Number of males	5		5		5		5	
Urine volume (mL/24hr)	12.5	± 5.8	23.1	± 10.9	13.8	± 4.1	23.2	± 12.0
Specific gravity	1.063	± 0.015	1.037	± 0.014	1.054	± 0.013	1.051	± 0.017
Electrolyte, density								
Na(mEq/L)	98.9	± 17.4	73.0	± 39.0	118.1	± 28.4	96.3	± 30.5
K(mEq/L)	245.22	± 37.30	161.05	± 61.27	225.07	± 65.21	186.79	± 58.15
Cl(mEq/L)	147.6	± 32.3	105.7	± 50.7	149.2	± 35.4	116.9	± 36.4
Electrolyte, gross volume								
Na(mEq/24hr)	1.19	± 0.48	1.44	± 0.38	1.59	± 0.39	1.97	± 0.47
K(mEq/24hr)	2.93	± 0.97	3.25	± 0.28	2.95	± 0.57	3.79	± 0.67
Cl(mEq/24hr)	1.81	± 0.73	2.08	± 0.37	1.98	± 0.40	2.43	± 0.67

Each value shows mean ± S.D.

Table 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Urinalysis of females

Group	Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of females	5	5	5	5
pH				
6.0	1	0	3	0
6.5	2	3	1	0
7.0	1	1	0	3
7.5	1	0	0	1
8.0	0	1	0	1
8.5	0	0	1	0
Protein				
- (negative)	0	0	1	1
± (10 ≤ and < 30 mg/dL)	3	1	1	3
+ (30 ≤ and < 100 mg/dL)	2	4	3	1
Glucose				
- (negative)	5	5	5	5
Ketone				
- (negative)	2	1	1	5
± (5 ≤ and < 10 mg/dL)	3	4	3	0
+ (10 ≤ and < 40 mg/dL)	0	0	1	0
Bilirubin				
- (negative)	5	5	5	5
Occult blood				
- (negative)	5	5	5	5
Urobilinogen				
± (normal)	3	2	3	5
+ (2.0 ≤ and < 4.0 mg/dL)	2	3	1	0
2+ (4.0 ≤ and < 8.0 mg/dL)	0	0	1	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	5
White Blood cells				
- (not observed)	5	5	5	5
Casts				
- (not observed)	5	5	5	5
Cristals				
- (not observed)	2	1	2	1
± (a few)	3	4	3	4
Epithelial cells				
- (not observed)	5	4	5	5
± (a few)	0	1	0	0

Table 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of females

Group	Control (vehicle: corn oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
Number of females	5		5		5		5	
Urine volume (mL/24hr)	7.0 ±	2.1	8.0 ±	1.9	11.6 ±	7.0	26.4 ±	14.8 **
Specific gravity	1.058 ±	0.015	1.064 ±	0.007	1.044 ±	0.019	1.036 ±	0.023
Electrolyte, density								
Na(mEq/L)	126.6 ±	55.1	132.6 ±	28.2	93.1 ±	25.8	65.3 ±	43.7
K(mEq/L)	222.03 ±	85.90	274.21 ±	79.88	153.10 ±	84.09	136.23 ±	100.01
Cl(mEq/L)	154.6 ±	69.6	174.6 ±	40.3	114.5 ±	72.1	89.2 ±	70.8
Electrolyte, gross volume								
Na(mEq/24hr)	0.83 ±	0.35	1.05 ±	0.26	0.98 ±	0.37	1.21 ±	0.46
K(mEq/24hr)	1.53 ±	0.80	2.23 ±	0.89	1.63 ±	0.87	2.43 ±	1.03
Cl(mEq/24hr)	1.05 ±	0.59	1.42 ±	0.51	1.19 ±	0.66	1.52 ±	0.89

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 2-butoxyethyl acetate in rats
 Hematological analysis of males

Group		Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)
Number of males		10	10	10	9
RBC	10000/ μ L	816 \pm 40	805 \pm 42	763 \pm 60 *	506 \pm 36 **
HGB	g/dL	14.4 \pm 0.6	13.9 \pm 0.6	13.6 \pm 0.8 *	10.6 \pm 0.7 **
Hematocrit	%	43.6 \pm 1.8	42.6 \pm 1.9	42.0 \pm 2.5	36.7 \pm 2.0 **
MCV	fL	53.4 \pm 2.2	53.0 \pm 1.5	55.2 \pm 3.6	72.7 \pm 3.2 **
MCH	pg	17.6 \pm 0.7	17.3 \pm 0.6	17.8 \pm 0.9	20.9 \pm 0.8 **
MCHC	g/dL	33.0 \pm 0.3	32.7 \pm 0.4	32.3 \pm 0.7	28.8 \pm 0.7 **
Platelet	10000/ μ L	97.2 \pm 15.7	100.0 \pm 11.1	99.3 \pm 8.3	89.2 \pm 8.1
PT	sec.	16.5 \pm 1.1	16.0 \pm 2.5	15.5 \pm 1.5	13.5 \pm 0.9 **
APTT	sec.	16.9 \pm 3.1	15.4 \pm 3.2	16.0 \pm 2.5	14.4 \pm 3.4
WBC	100/ μ L	77.4 \pm 24.7	73.6 \pm 23.2	71.2 \pm 30.6	58.0 \pm 8.0
Neutrophil	%	19.1 \pm 6.1	17.5 \pm 3.0	16.5 \pm 5.6	12.0 \pm 5.1 *
Eosinophil	%	1.3 \pm 0.4	1.3 \pm 0.4	1.3 \pm 0.6	0.0 \pm 0.1 **
Basophil	%	0.1 \pm 0.1	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Monocyte	%	3.9 \pm 1.2	4.0 \pm 0.6	3.4 \pm 0.9	2.8 \pm 1.4
Lymphocyte	%	75.7 \pm 6.1	77.1 \pm 3.1	78.8 \pm 6.6	85.1 \pm 6.2 **
Reticulocyte	%	3.14 \pm 0.47	3.07 \pm 0.39	4.01 \pm 1.09	15.27 \pm 3.88 **

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 2-butoxyethyl acetate in rats
Hematological analysis of females

Group		Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)	
Number of females		10	10	10	10	
RBC	10000/ μ L	742 \pm 28	723 \pm 26	634 \pm 25	**	425 \pm 31 **
HGB	g/dL	13.8 \pm 0.5	13.4 \pm 0.4	12.4 \pm 0.3	**	10.0 \pm 0.4 **
Hematocrit	%	41.1 \pm 1.6	40.5 \pm 1.3	38.9 \pm 1.1	**	38.6 \pm 1.6 **
MCV	fL	55.4 \pm 1.5	56.1 \pm 2.4	61.4 \pm 2.9	*	91.2 \pm 5.0 **
MCH	pg	18.6 \pm 0.4	18.5 \pm 0.6	19.5 \pm 0.5	**	23.7 \pm 0.9 **
MCHC	g/dL	33.5 \pm 0.3	33.0 \pm 0.4	31.8 \pm 0.8	**	26.0 \pm 0.9 **
Platelet	10000/ μ L	93.4 \pm 8.6	92.1 \pm 7.8	89.0 \pm 8.9		77.8 \pm 8.8 **
PT	sec.	11.9 \pm 0.6	11.6 \pm 0.3	11.8 \pm 0.6		13.0 \pm 1.3 *
APTT	sec.	11.1 \pm 1.8	11.1 \pm 1.8	10.5 \pm 1.5		11.8 \pm 2.0 (9)
WBC	100/ μ L	52.2 \pm 17.8	47.8 \pm 9.4	46.2 \pm 12.6		43.3 \pm 8.9
Neutrophil	%	11.1 \pm 4.1	15.2 \pm 4.9	11.6 \pm 2.5		13.0 \pm 4.1
Eosinophil	%	1.6 \pm 0.5	1.5 \pm 0.7	1.1 \pm 0.5		0.3 \pm 0.2 **
Basophil	%	0.0 \pm 0.0	0.0 \pm 0.1	0.0 \pm 0.1		0.0 \pm 0.0
Monocyte	%	3.0 \pm 1.1	3.2 \pm 0.8	3.5 \pm 1.4		2.4 \pm 0.8
Lymphocyte	%	84.3 \pm 4.8	80.0 \pm 4.6	83.8 \pm 3.8		84.3 \pm 3.9
Reticulocyte	%	2.75 \pm 0.50	2.75 \pm 0.51	5.62 \pm 1.87	*	22.22 \pm 3.73 **

Each value shows mean \pm S.D.

Figures in parentheses indicate number of males.

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

Table 7
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Blood biochemical analysis of males

Group		Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)	
Number of males		10	10	10	9	
Total protein	g/dL	5.5 ± 0.3	5.4 ± 0.3	5.3 ± 0.3	5.2 ± 0.2	
Albumin	g/dL	3.5 ± 0.1	3.5 ± 0.2	3.4 ± 0.2	3.5 ± 0.1	
A/G		1.76 ± 0.18	1.81 ± 0.13	1.77 ± 0.19	2.13 ± 0.18	**
Glucose	mg/dL	142 ± 18	151 ± 22	144 ± 14	133 ± 10	
Total cholesterol	mg/dL	48 ± 9	47 ± 10	50 ± 13	34 ± 5	*
Triglyceride	mg/dL	68 ± 22	49 ± 20	49 ± 29	37 ± 8	**
AST	U/L	63 ± 15	58 ± 9	56 ± 8	66 ± 5	
ALT	U/L	31 ± 10	28 ± 4	27 ± 5	32 ± 4	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
CPK	U/L	369 ± 260	241 ± 126	266 ± 208	270 ± 124	
BUN	mg/dL	11.4 ± 1.6	11.6 ± 1.2	11.2 ± 1.1	12.1 ± 2.1	
Creatinine	mg/dL	0.31 ± 0.04	0.30 ± 0.05	0.33 ± 0.04	0.36 ± 0.05	
Total bilirubin	mg/dL	0.05 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	**
ALP	U/L	403 ± 105	411 ± 73	494 ± 196	493 ± 112	
Inorganic phosphorus	mg/dL	5.9 ± 0.6	5.7 ± 0.6	6.2 ± 0.6	6.8 ± 0.7	**
Ca	mg/dL	9.1 ± 0.2	9.1 ± 0.2	9.0 ± 0.2	8.8 ± 0.2	**
Na	mEq/L	145.0 ± 0.9	145.0 ± 0.9	144.5 ± 0.6	144.9 ± 0.8	
K	mEq/L	3.88 ± 0.13	3.93 ± 0.12	4.08 ± 0.15	4.12 ± 0.25	**
Cl	mEq/L	106.3 ± 1.8	105.8 ± 1.8	105.6 ± 1.1	106.6 ± 1.5	

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 2-butoxyethyl acetate in rats

Blood biochemical analysis of females

Group		Control (vehicle: corn oil)	Low dose (BEA 20 mg/kg)	Medium dose (BEA 100 mg/kg)	High dose (BEA 500 mg/kg)	
		10	10	10	10	
Total protein	g/dL	5.9 ± 0.4	6.0 ± 0.3	5.9 ± 0.4	5.3 ± 0.4	**
Albumin	g/dL	4.0 ± 0.3	4.1 ± 0.3	4.0 ± 0.3	3.7 ± 0.3	*
A/G		2.22 ± 0.14	2.13 ± 0.2	2.11 ± 0.09	2.22 ± 0.24	
Glucose	mg/dL	133 ± 19	129 ± 9	131 ± 20	121 ± 9	
Total cholesterol	mg/dL	56 ± 8	62 ± 10	60 ± 14	51 ± 11	
Triglyceride	mg/dL	20 ± 7	35 ± 17	29 ± 17	20 ± 8	
AST	U/L	49 ± 5	52 ± 8	54 ± 5	69 ± 11	**
ALT	U/L	20 ± 2	21 ± 3	24 ± 3	32 ± 8	**
γ-GTP	U/L	0 ± 1	1 ± 1	0 ± 1	1 ± 0	
CPK	U/L	180 ± 77	330 ± 235	195 ± 96	161 ± 57	
BUN	mg/dL	13.9 ± 1.0	13.1 ± 1.3	13.9 ± 1.9	16.0 ± 3.2	
Creatinine	mg/dL	0.42 ± 0.07	0.38 ± 0.03	0.39 ± 0.04	0.37 ± 0.05	
Total bilirubin	mg/dL	0.08 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	**
ALP	U/L	252 ± 79	257 ± 99	264 ± 66	300 ± 65	
Inorganic phosphorus	mg/dL	5.5 ± 1.1	5.7 ± 1.0	6.2 ± 0.9	7.0 ± 0.8	**
Ca	mg/dL	9.3 ± 0.6	9.5 ± 0.6	9.6 ± 0.5	9.0 ± 0.6	
Na	mEq/L	144.8 ± 1.4	145.7 ± 1.0	145.7 ± 1.0	145.6 ± 1.0	
K	mEq/L	4.15 ± 0.42	4.12 ± 0.36	4.21 ± 0.21	3.98 ± 0.25	
Cl	mEq/L	108.2 ± 1.4	108.8 ± 1.5	108.5 ± 2.0	109.8 ± 1.2	

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 2-butoxyethyl acetate in rats
Organ weight of males

Group		Control (vehicle: com oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
Number of males		10		10		10		9	
Body weight	(g)	596.6 ± 58.9		577.7 ± 58.3		562.8 ± 63.7		514.6 ± 30.3 **	
Brain	(mg)	2045.3 ± 90.9		2028.7 ± 70.7		2032.1 ± 79.6		2026.3 ± 54.0	
	(mg/g)	3.453 ± 0.314		3.547 ± 0.412		3.648 ± 0.394		3.950 ± 0.256 *	
Thy mus	(mg)	283.6 ± 55.7		287.2 ± 85.0		303.9 ± 79.2		274.4 ± 69.4	
	(mg/g)	0.478 ± 0.096		0.499 ± 0.147		0.543 ± 0.138		0.533 ± 0.136	
Heart	(mg)	1616.9 ± 148.6		1569.6 ± 100.5		1574.9 ± 176.5		1524.7 ± 97.2	
	(mg/g)	2.715 ± 0.144		2.733 ± 0.232		2.806 ± 0.204		2.967 ± 0.170 *	
Lungs	(mg)	1468.0 ± 95.9		1431.3 ± 94.9		1432.3 ± 107.5		1395.7 ± 102.7	
	(mg/g)	2.478 ± 0.242		2.490 ± 0.177		2.560 ± 0.205		2.716 ± 0.190	
Liver	(mg)	16403.1 ± 2655.8		15939.1 ± 2459.0		14710.8 ± 1920.0		16217.9 ± 1556.6	
	(mg/g)	27.379 ± 2.419		27.529 ± 2.510		26.148 ± 1.770		31.487 ± 1.959 **	
Kidney (R)	(mg)	1677.4 ± 150.0		1657.6 ± 169.9		1668.5 ± 226.9		1794.7 ± 200.8	
	(mg/g)	2.824 ± 0.261		2.889 ± 0.347		2.975 ± 0.381		3.488 ± 0.333 **	
Kidney (L)	(mg)	1704.0 ± 129.4		1641.3 ± 176.7		1681.4 ± 220.4		1833.7 ± 209.4	
	(mg/g)	2.872 ± 0.258		2.857 ± 0.321		2.996 ± 0.330		3.561 ± 0.326 **	
Kidney	(mg)	3381.4 ± 272.6		3298.9 ± 337.4		3349.9 ± 442.2		3628.3 ± 403.7	
	(mg/g)	5.696 ± 0.507		5.746 ± 0.654		5.971 ± 0.701		7.049 ± 0.644 **	
Spleen	(mg)	827.6 ± 95.7		806.1 ± 97.6		833.6 ± 109.9		1272.1 ± 236.4 **	
	(mg/g)	1.392 ± 0.154		1.396 ± 0.109		1.489 ± 0.186		2.459 ± 0.332 **	
Testis (R)	(mg)	1802.5 ± 128.4		1770.8 ± 167.3		1707.2 ± 109.2		1701.3 ± 137.8	
	(mg/g)	3.045 ± 0.346		3.083 ± 0.326		3.061 ± 0.332		3.308 ± 0.227	
Testis (L)	(mg)	1780.3 ± 100.8		1733.6 ± 158.4		1719.1 ± 127.4		1704.6 ± 136.4	
	(mg/g)	3.009 ± 0.326		3.021 ± 0.339		3.084 ± 0.375		3.315 ± 0.232	
Testis	(mg)	3582.8 ± 221.8		3504.4 ± 323.9		3426.3 ± 233.5		3405.9 ± 271.6	
	(mg/g)	6.054 ± 0.663		6.103 ± 0.662		6.145 ± 0.703		6.623 ± 0.454	
Prostate, ventral	(mg)	500.2 ± 155.5		590.3 ± 114.2		627.9 ± 181.5		580.2 ± 139.7	
	(mg/g)	0.855 ± 0.310		1.026 ± 0.199		1.129 ± 0.362		1.132 ± 0.282	
Submandibular glands	(mg)	787.3 ± 141.7		717.1 ± 78.6		748.0 ± 94.6		636.2 ± 72.8 **	
	(mg/g)	1.318 ± 0.171		1.248 ± 0.139		1.337 ± 0.175		1.238 ± 0.139	
Seminal vesicles	(mg)	1810.3 ± 163.4		1642.5 ± 262.2		1693.7 ± 282.2		1706.1 ± 211.7	
	(mg/g)	3.053 ± 0.334		2.850 ± 0.406		3.027 ± 0.469		3.311 ± 0.320	

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 2-butoxyethyl acetate in rats

Organ weight of males

Group		Control (vehicle: corn oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
Number of males		10		10		10		9	
Body weight	(g)	596.6 ±	58.9	577.7 ±	58.3	562.8 ±	63.7	514.6 ±	30.3 **
Pituitary gland	(mg)	13.3 ±	2.1	12.4 ±	1.9	13.0 ±	2.4	11.4 ±	1.7
	(mg/g)	0.023 ±	0.005	0.021 ±	0.003	0.023 ±	0.005	0.022 ±	0.004
Thyroid gland	(mg)	26.5 ±	5.4	25.3 ±	2.3	26.5 ±	6.6	28.2 ±	5.6
	(mg/g)	0.045 ±	0.009	0.044 ±	0.006	0.047 ±	0.009	0.055 ±	0.014
Adrenal gland (R)	(mg)	28.2 ±	4.1	(9) 28.4 ±	5.9	24.7 ±	3.3	24.4 ±	3.9
	(mg/g)	0.470 ±	0.007	(9) 0.049 ±	0.009	0.044 ±	0.007	0.048 ±	0.008
Adrenal gland (L)	(mg)	29.9 ±	4.9	(9) 30.0 ±	6.3	25.6 ±	3.1	25.8 ±	4.0
	(mg/g)	0.050 ±	0.010	(9) 0.052 ±	0.010	0.046 ±	0.006	0.050 ±	0.009
Adrenal gland	(mg)	58.1 ±	8.6	(9) 58.4 ±	11.8	50.3 ±	6.1	50.2 ±	7.7
	(mg/g)	0.098 ±	0.017	(9) 0.101 ±	0.018	0.090 ±	0.013	0.098 ±	0.016

Each value shows mean ± S.D.

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

Figures in parentheses indicate number of cases.

Table 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Organ weight of females

Group	Control (vehicle: corn oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
		10	10	10	10	10	10	10
Number of females		10	10	10	10	10	10	10
Body weight	(g)	274.7 ± 27.8	287.0 ± 34.0	279.3 ± 30.1	274.6 ± 19.6			
Brain	(mg)	1854.2 ± 67.3	1821.9 ± 71.1	1876.2 ± 81.5	1826.8 ± 91.9			
	(mg/g)	6.811 ± 0.716	6.433 ± 0.841	6.771 ± 0.586	6.677 ± 0.495			
Thymus	(mg)	234.2 ± 61.7	223.6 ± 53.0	281.0 ± 96.8	243.8 ± 55.6			
	(mg/g)	0.870 ± 0.294	0.776 ± 0.137	1.007 ± 0.347	0.886 ± 0.190			
Heart	(mg)	861.0 ± 65.0	893.1 ± 95.1	890.7 ± 69.2	937.3 ± 99.2			
	(mg/g)	3.148 ± 0.221	3.125 ± 0.259	3.205 ± 0.227	3.411 ± 0.247 *			
Lungs	(mg)	1016.9 ± 79.5	1045.1 ± 55.4	1047.5 ± 72.0	1055.6 ± 90.9			
	(mg/g)	3.720 ± 0.310	3.678 ± 0.382	3.779 ± 0.367	3.844 ± 0.189			
Liver	(mg)	6739.3 ± 623.5	7392.0 ± 1046.9	7870.8 ± 828.2 *	9742.3 ± 813.6 **			
	(mg/g)	24.613 ± 1.773	25.720 ± 1.366	28.239 ± 1.765 **	35.491 ± 2.012 **			
Kidney (R)	(mg)	865.0 ± 72.1	906.6 ± 96.4	941.3 ± 84.0	1024.5 ± 101.6 **			
	(mg/g)	3.161 ± 0.230	3.170 ± 0.206	3.383 ± 0.228	3.731 ± 0.247 **			
Kidney (L)	(mg)	848.9 ± 67.8	883.0 ± 79.3	914.2 ± 81.5	1008.3 ± 93.6 **			
	(mg/g)	3.103 ± 0.218	3.091 ± 0.209	3.286 ± 0.227	3.670 ± 0.192 **			
Kidney	(mg)	1713.9 ± 136.4	1789.6 ± 172.8	1855.4 ± 163.4	2032.7 ± 192.8 **			
	(mg/g)	6.264 ± 0.434	6.261 ± 0.399	6.668 ± 0.445	7.401 ± 0.428 **			
Spleen	(mg)	526.8 ± 83.9	494.9 ± 82.3	601.4 ± 74.3	1019.5 ± 206.2 **			
	(mg/g)	1.921 ± 0.264	1.725 ± 0.206	2.173 ± 0.323	3.692 ± 0.568 **			
Ovary (R)	(mg)	38.1 ± 10.3	40.4 ± 10.1	41.9 ± 6.8	36.2 ± 3.2			
	(mg/g)	0.139 ± 0.034	0.141 ± 0.033	0.151 ± 0.024	0.132 ± 0.011			
Ovary (L)	(mg)	35.9 ± 6.8	39.0 ± 9.4	40.1 ± 9.7	33.8 ± 3.3			
	(mg/g)	0.132 ± 0.028	0.136 ± 0.030	0.144 ± 0.034	0.124 ± 0.015			
Ovary	(mg)	74.1 ± 12.8	79.4 ± 18.9	82.0 ± 14.9	70.0 ± 5.1			
	(mg/g)	0.271 ± 0.045	0.277 ± 0.061	0.295 ± 0.052	0.256 ± 0.022			
Uterus	(mg)	603.1 ± 215.7	535.2 ± 142.1	541.8 ± 186.6	537.8 ± 156.8			
	(mg/g)	2.253 ± 0.969	1.859 ± 0.399	1.993 ± 0.833	1.951 ± 0.528			
Submandibular glands	(mg)	433.8 ± 38.1	445.7 ± 33.8	424.5 ± 25.7	416.7 ± 36.2			
	(mg/g)	1.593 ± 0.200	1.569 ± 0.195	1.531 ± 0.131	1.522 ± 0.150			

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 2-butoxyethyl acetate in rats

Organ weight of females

Group		Control (vehicle: corn oil)		Low dose (BEA 20 mg/kg)		Medium dose (BEA 100 mg/kg)		High dose (BEA 500 mg/kg)	
		10		10		10		10	
Number of females		10		10		10		10	
Body weight	(g)	274.7 ± 27.8		287.0 ± 34.0		279.3 ± 30.1		274.6 ± 19.6	
Pituitary gland	(mg)	16.3 ± 3.2		16.8 ± 3.0		17.0 ± 2.2		14.2 ± 1.2	
	(mg/g)	0.060 ± 0.012		0.059 ± 0.009		0.061 ± 0.008		0.052 ± 0.007	
Thyroid gland	(mg)	23.6 ± 5.8		20.3 ± 2.3		19.7 ± 2.8		20.8 ± 4.0	
	(mg/g)	0.086 ± 0.018		0.071 ± 0.010		0.071 ± 0.011		0.076 ± 0.016	
Adrenal gland (R)	(mg)	26.7 ± 4.1		28.0 ± 3.4		30.2 ± 3.6		28.3 ± 5.0	
	(mg/g)	0.098 ± 0.019		0.098 ± 0.006		0.109 ± 0.011		0.103 ± 0.013	
Adrenal gland (L)	(mg)	27.5 ± 2.8		28.9 ± 4.6		30.2 ± 3.3		31.0 ± 4.5	
	(mg/g)	0.101 ± 0.015		0.101 ± 0.010		0.109 ± 0.012		0.113 ± 0.013	
Adrenal gland	(mg)	54.2 ± 6.2		56.8 ± 7.9		60.4 ± 6.5		59.3 ± 9.3	
	(mg/g)	0.199 ± 0.032		0.198 ± 0.014		0.218 ± 0.022		0.215 ± 0.025	

Each value shows mean ± S.D.

Table 9
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Macroscopic findings of males

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)		BEA 20		BEA 100		BEA 500	
		-	P	-	P	-	P	-	P
Brain									
Recessed area		10	0	10	0	9	1	9	0
Ileum									
Diverticulum		10	0	10	0	10	0	7	2
Kidney									
Pale colored area		10	0	10	0	10	0	8	1
Skull									
Elevated area		10	0	10	0	9	1	9	0
Spleen									
Discoloration, dark colored		10	0	10	0	8	2	0	9
Enlargement		10	0	10	0	10	0	1	8
Stomach									
Thickening, mucosa		10	0	10	0	9	1	2	7
Thymus									
Small		10	0	10	0	10	0	8	1

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 2-butoxyethyl acetate in rats

Macroscopic findings of females

Findings	Group	Control (vehicle: corn oil)		BEA		BEA		BEA	
	Dose (mg/kg)	0		20		100		500	
Grade		-	P	-	P	-	P	-	P
Spleen									
Discoloration, dark colored		10	0	10	0	10	0	0	10
Enlargement		10	0	10	0	10	0	1	9
Stomach									
Thickening, mucosa		10	0	10	0	10	0	6	4

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Table 10
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA								BEA															
		0								20								100								500							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE				
Brain																																	
Cellular infiltration, mononuclear cell		10	0	0	0	0																											
Deposit, pigment, brown		10	0	0	0	0																											
Thickening, meninx		10	0	0	0	0																											
Spinal cord		10																															
Pituitary gland																																	
Cyst		8																															
Cyst-like lesion		9																															
Eyeball																																	
Dysplasia, retina		9																															
Mineralization		9	1	0	0	0																											
Harderian gland																																	
Cellular infiltration, lymphocyte		8	2	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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA								BEA								BEA										
		0								20								100								500										
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Nasal cavity																																				
Eosinophilic globule		5	4	1	0	0																	7	2	0	0	0									
Mineralization		5	5	0	0	0																	2	6	1	0	0									
Necrosis, focal		10	0	0	0	0																	7	2	0	0	0									
Zymbal gland																																				
Dilatation, cystic		9	1	0	0	0																	8	0	1	0	0									
Submandibular gland		10																					9													
Sublingual gland		10																					9													
Tongue		10																					9													
Esophagus		10																					9													
Trachea		10																					9													
Aorta		10																					9													
Thyroid gland																																				
Ultimobranchial body		8					2																6						3							
Parathyroid 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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA																	
		0								20				100				500									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+
Liver																											
Deposit, hemosiderin		10	0	0	0	0		10	0	0	0	0		8	2	0	0	0		**,#	0	6	3	0	0		
Fatty change, hepatocyte		0	3	1	5	1		0	1	2	7	0		1	2	5	2	0		**,#	5	4	0	0	0		
Hypertrophy, hepatocyte		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		*,#	4	5	0	0	0		
Microgranuloma		6	3	1	0	0		8	2	0	0	0		6	4	0	0	0			6	1	2	0	0		
Tension lipidosis		10				0		10				0		10				0			7					2	
Kidney																											
Basophilic tubule, cortex		6	4	0	0	0		5	5	0	0	0		8	2	0	0	0			9	0	0	0	0		
Cellular infiltration, lymphocyte		9	1	0	0	0		9	1	0	0	0		10	0	0	0	0			8	1	0	0	0		
Deposit, hemosiderin		10	0	0	0	0		10	0	0	0	0		10	0	0	0	0		**,#	0	8	1	0	0		
Hemorrhage		9	1	0	0	0		10	0	0	0	0		10	0	0	0	0			9	0	0	0	0		
Mineralization		7	3	0	0	0		8	2	0	0	0		8	2	0	0	0			8	1	0	0	0		
Spleen																											
Deposit, hemosiderin		0	5	5	0	0		0	6	4	0	0		*	0	0	8	2	0	**	0	0	0	9	0		
Hematopoiesis, extramedullary		0	1	8	1	0		0	0	9	1	0		0	0	7	3	0		**	0	0	0	5	4		

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 (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA 20				BEA 100				BEA 500												
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Lymph node, submandibular		10																9												
Lymph node, mesenteric		10																9												
Testis		10																9												
Epididymis																														
Cellular infiltration, lymphocyte		10	0	0	0	0											8	1	0	0	0									
Prostate																														
Cellular infiltration, lymphocyte		3	5	2	0	0											7	0	2	0	0									
Seminal vesicle		10																9												
Coagulating gland		10																9												
Urinary bladder																														
Cellular infiltration, lymphocyte		9	1	0	0	0											9	0	0	0	0									
Femur		10																9												
Marrow, femur																														
Hematopoiesis, increased		10	0	0	0	0			10	0	0	0	0			8	2	0	0	0			**##	0	2	5	2	0		
Sternum		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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

##P<0.05, ###P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)							BEA							BEA							BEA						
		0							20							100							500						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		10																											
Spinal cord		10																											
Pituitary gland		10																											
Eyeball		10																											
Harderian gland																													
Cellular infiltration, lymphocyte		9	1	0	0	0																	8	2	0	0	0		
Optic nerve		10																											
Nasal cavity																													
Cellular infiltration, neutrophil		10	0	0	0	0																	8	2	0	0	0		
Eosinophilic globule		6	3	1	0	0																	5	5	0	0	0		
Mineralization		9	1	0	0	0																	7	3	0	0	0		
Necrosis, focal		10	0	0	0	0																	8	1	1	0	0		
Zymbal gland		10																											
Submandibular gland																													
Hypertrophy, acinar cell		10	0	0	0	0																	9	0	1	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 (Mann-Whitney U test).

##P<0.05, ###P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)
 Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)							BEA							BEA													
		0							20							100							500						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Sublingual gland																													
Hypertrophy, acinar cell		10	0	0	0	0																	9	1	0	0	0		
Tongue		10																					10						
Esophagus		10																					10						
Trachea		10																					10						
Aorta		10																					10						
Thyroid gland																													
Ectopic thymic tissue		7					3																10					0	
Ultimobranchial body		3					7																5					5	
Parathyroid gland		10																					10						
Thymus																													
Hyperplasia, epithelial tubule/cord		7	3	0	0	0																	5	5	0	0	0		
Heart																													
Cellular infiltration, mononuclear cell		10	0	0	0	0																	8	2	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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of females

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA								BEA															
		0								20								100								500							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE				
Kidney																																	
Basophilic tubule, cortex		6	4	0	0	0	7	3	0	0	0	8	2	0	0	0	#	10	0	0	0	0											
Cellular infiltration, lymphocyte		7	3	0	0	0	9	1	0	0	0	9	1	0	0	0	10	0	0	0	0	0											
Cyst		9				1	9				1	10				0	10					0											
Deposit, hemosiderin		10	0	0	0	0	10	0	0	0	0	7	3	0	0	0	**,#	0	7	3	0	0											
Hyperplasia, transitional cell		9	1	0	0	0	9	1	0	0	0	10	0	0	0	0	10	0	0	0	0	0											
Mineralization		3	6	1	0	0	4	4	2	0	0	#	8	2	0	0	0	*,##	9	1	0	0	0										
Spleen																																	
Congestion		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	9	0	1	0	0	0											
Deposit, hemosiderin		0	0	4	6	0	0	0	4	6	0	0	0	1	9	0	**	0	0	0	5	5											
Hematopoiesis, extramedullary		0	4	6	0	0	0	6	4	0	0	0	0	8	2	0	**	0	0	1	9	0											
Pancreas		10															10																
Adrenal gland		10															10																
Stomach																																	
Edema, lamina propria		8	2	0	0	0	6	3	1	0	0	6	1	3	0	0	6	2	2	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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of females

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA				BEA				BEA				
		0								20				100				500				
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Duodenum		10																				
Jejunum		10																				
Ileum		10																				
Cecum		10																				
Colon		10																				
Rectum		10																				
Lymph node, submandibular		10																				
Lymph node, mesenteric		10																				
Ovary																						
Mineralization		10	0	0	0	0												9	1	0	0	0
Oviduct		10																				
Uterus		10																				
Vagina		10																				
Urinary bladder		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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Table 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Findings	Group Dose (mg/kg) Grade	Control (vehicle: corn oil)								BEA				BEA				BEA													
		0								20				100				500													
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE		
Femur		10																10													
Marrow, femur																															
Hematopoiesis, increased		10	0	0	0	0		10	0	0	0	0		7	2	1	0	0	**##	0	0	0	10	0							
Sternum		10																10													
Marrow, sternum																															
Hematopoiesis, increased		10	0	0	0	0		10	0	0	0	0		9	1	0	0	0	**##	0	0	1	9	0							
Skeletal muscle		10																10													
Sciatic nerve		10																10													
Skin		10																10													
Mammary gland		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.

*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).

#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

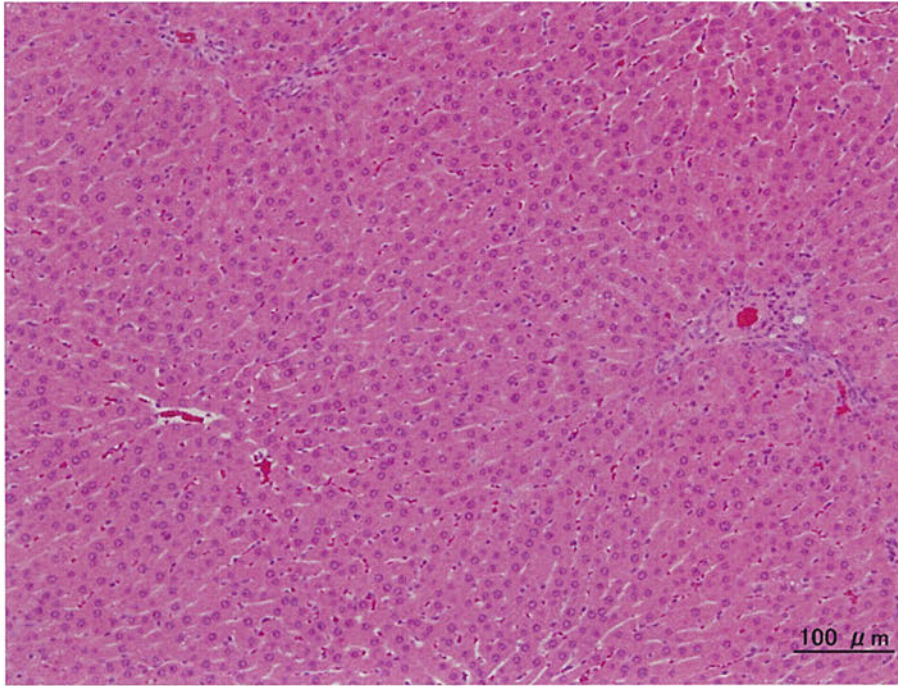


Photo 1

Microphotograph of the liver in the control group
(animal no. F01041), HE stain
No abnormal changes are observed.

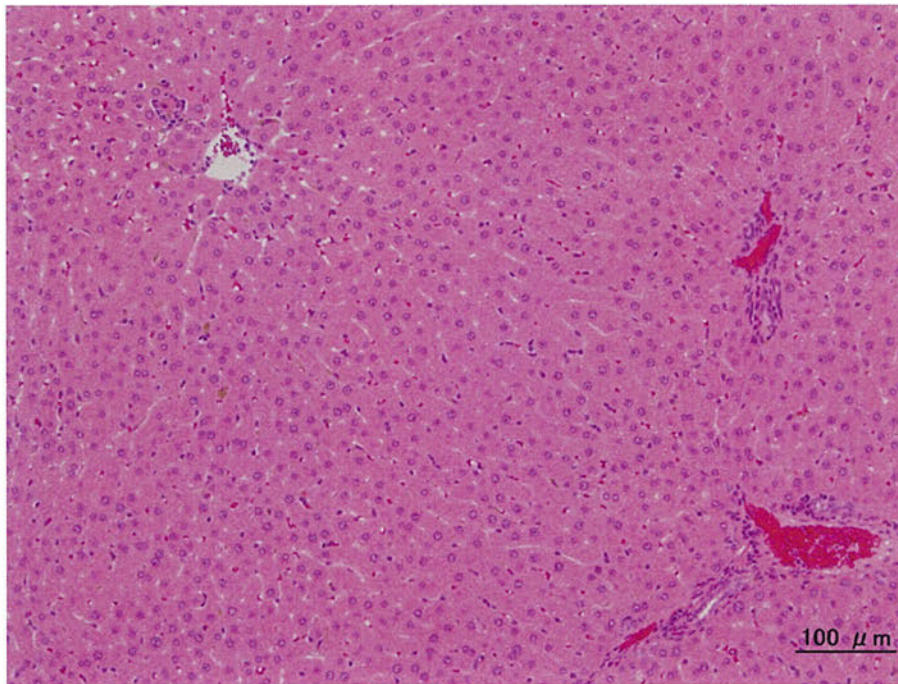


Photo 2

Microphotograph of the liver in the high dose group
(animal no. F04071), HE stain
Deposition of brown pigment (hemosiderin) in Kupffer cells and
hepatocellular hypertrophy in centrilobular/midzonal area are observed.

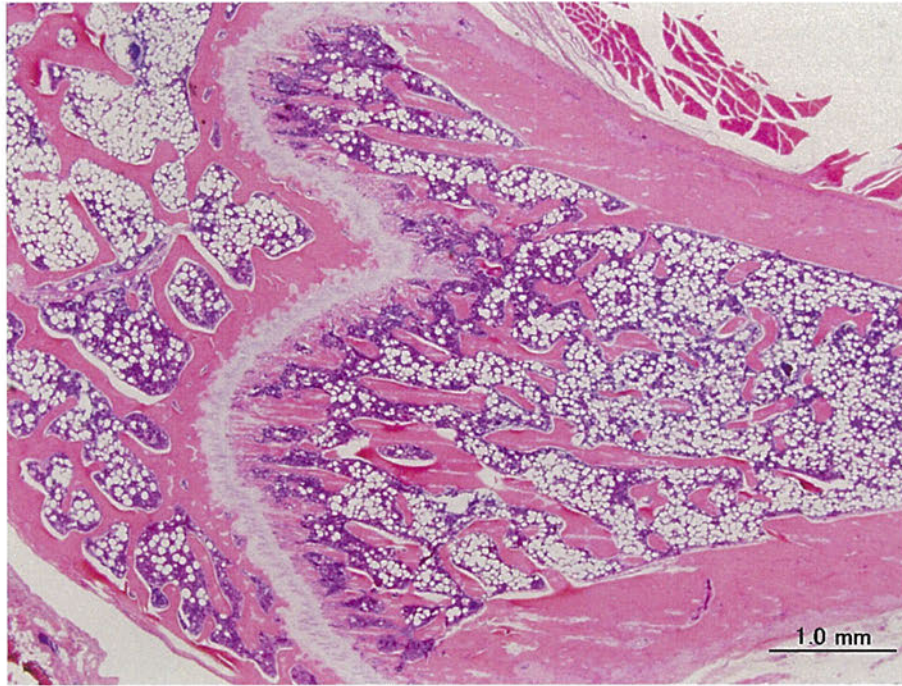


Photo 3

Microphotograph of the femoral bone marrow in the control group (animal no. M01001), HE stain
No abnormal changes are observed.

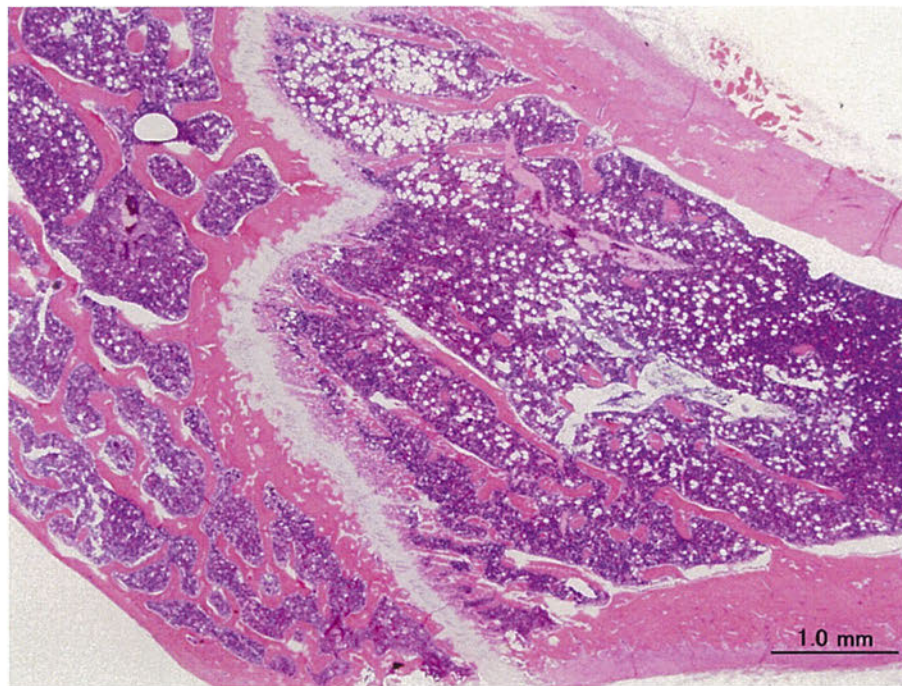


Photo 4

Microphotograph of the femoral bone marrow in the high dose group (animal no. M04034), HE stain
Hematopoietic cells are increased.

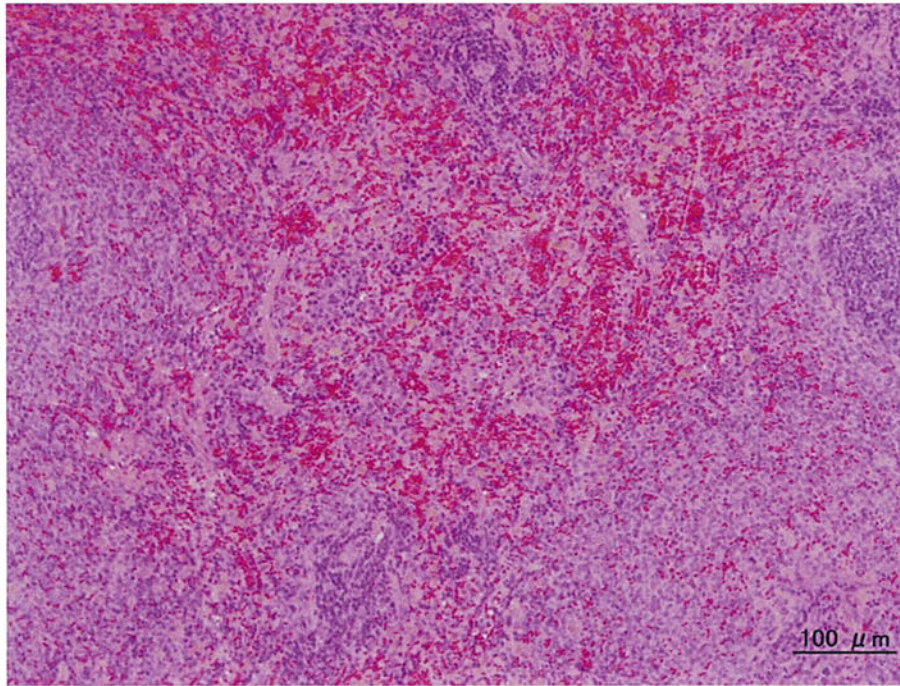


Photo 5

Microphotograph of the spleen in the control group (animal no. M01009), HE stain
Deposition of brown pigment (hemosiderin) and extramedullary hematopoiesis are observed.

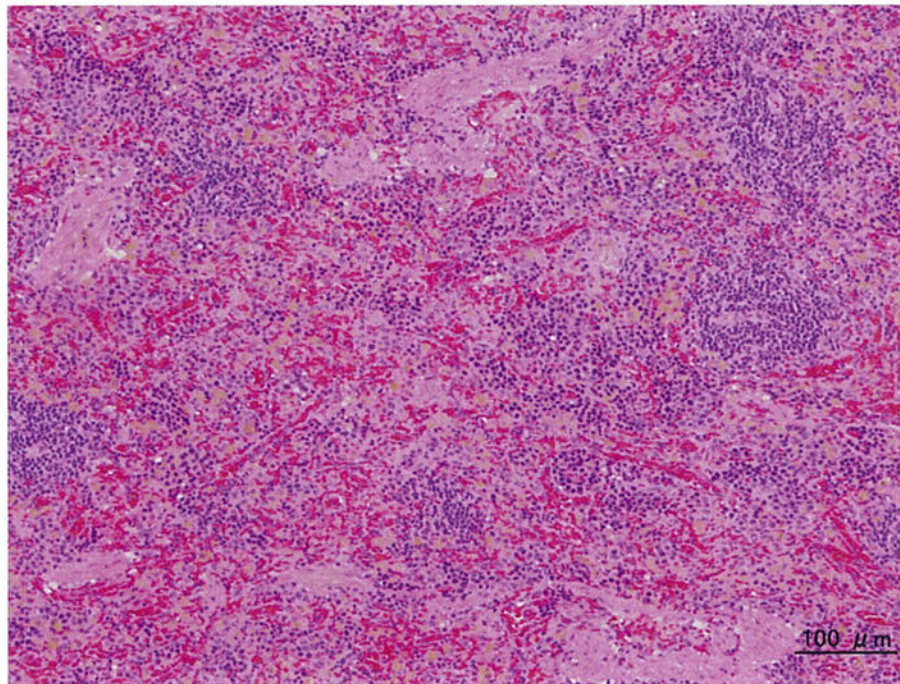


Photo 6

Microphotograph of the spleen in the high dose group (animal no. M04034), HE stain
Deposition of brown pigment (hemosiderin) and extramedullary hematopoiesis are increased.

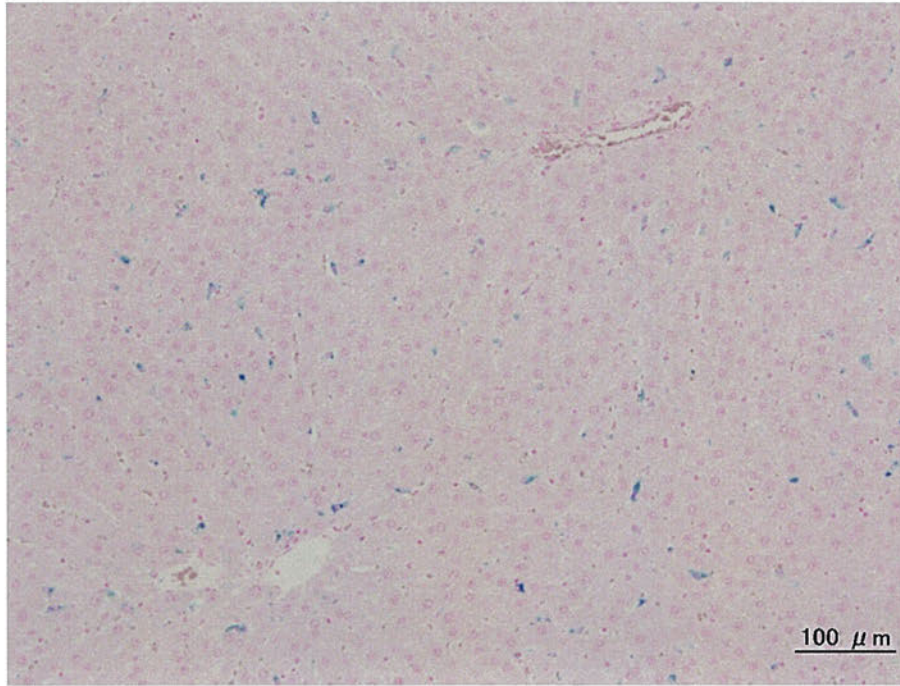


Photo 7

Microphotograph of the liver in the high dose group (animal no. M04034), Berlin blue stain
Cells positive for Berlin blue (hemosiderin) in Kupffer cells are observed.

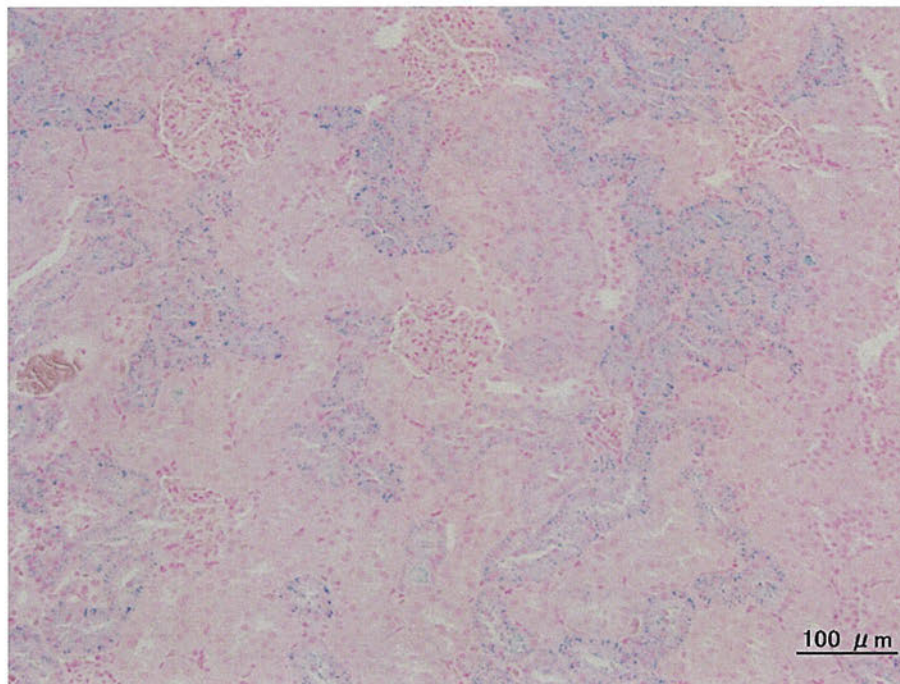


Photo 8

Microphotograph of the kidney in the high dose group (animal no. M04034), Berlin blue stain
Cells positive for Berlin blue (hemosiderin) in proximal tubules are observed.

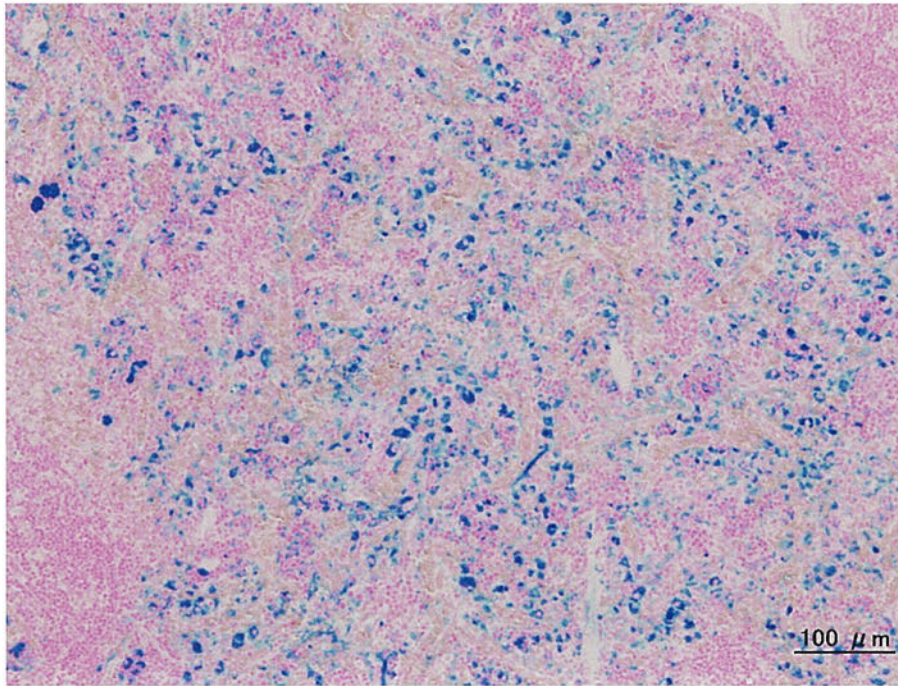


Photo 9

Microphotograph of the spleen in the high dose group
(animal no. M04034), Berlin blue stain
Cells positive for Berlin blue (hemosiderin) in red pulp are observed.

Appendix 2

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of males

Control (vehicle: corn oil)

Male No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	90
M01001	173.9	182.9	241.2	301.7	360.1	407.7	448.1	486.3	518.0	545.8	564.3	584.6	604.8	610.6	611.9
M01002	183.9	186.6	239.9	303.7	370.9	431.5	484.0	530.3	568.4	604.9	630.0	662.0	686.3	698.9	713.7
M01003	173.5	180.6	228.9	293.6	347.1	390.2	426.7	463.1	491.0	510.8	526.9	552.3	570.2	582.8	594.3
M01004	167.0	174.1	224.3	279.1	331.7	374.5	415.9	453.5	478.8	501.9	524.4	546.4	563.9	580.9	585.2
M01005	175.0	179.6	220.4	269.7	314.7	343.8	378.8	410.4	433.9	452.8	470.4	488.1	506.3	510.2	516.2
M01006	175.3	180.9	233.1	290.4	343.9	386.0	431.3	463.7	491.4	513.2	530.8	548.0	560.7	569.4	574.3
M01007	170.2	174.4	222.9	281.5	338.2	386.9	432.2	465.4	492.0	515.8	538.3	556.1	587.0	600.3	609.7
M01008	173.3	182.1	238.2	303.5	360.5	412.1	456.2	493.3	525.3	553.0	589.8	611.6	629.8	648.2	654.9
M01009	187.4	195.6	251.7	327.5	400.7	459.3	505.1	540.5	579.7	601.6	628.6	657.6	680.0	701.4	712.1
M01010	191.3	199.4	263.0	335.6	389.5	435.1	453.5	490.0	527.8	552.7	581.7	611.8	637.5	646.4	661.6
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	177.1	183.6	236.4	298.6	355.7	402.7	443.2	479.7	510.6	535.3	558.5	581.9	602.7	614.9	623.4
S.D.	7.8	8.2	13.5	20.7	26.3	33.6	35.3	37.7	43.0	46.4	50.2	54.4	56.5	59.7	62.4

Appendix 2 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of males

Low dose (BEA 20 mg/kg)

Male No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	90
M02011	176.1	183.5	232.5	292.2	343.6	389.6	426.1	453.2	474.9	491.3	496.8	512.8	529.1	543.1	557.8
M02012	162.9	168.5	216.7	267.6	318.7	360.8	395.2	426.8	453.3	477.0	490.2	506.8	529.0	547.0	554.3
M02013	190.5	201.1	265.6	335.7	400.2	449.5	494.2	530.4	557.4	573.9	586.9	615.1	624.7	644.7	637.5
M02014	175.7	184.7	237.5	301.4	359.5	403.4	456.9	495.1	531.5	501.8	547.3	579.7	609.8	635.4	637.7
M02015	177.9	187.4	249.4	317.5	378.4	424.2	466.2	502.4	520.7	534.6	548.4	561.9	573.4	588.2	595.9
M02016	181.4	189.6	244.4	303.2	350.2	387.9	425.5	456.3	487.6	511.8	525.8	545.4	565.9	581.1	588.9
M02017	179.2	189.5	237.8	311.8	393.8	456.3	508.9	549.4	583.7	609.8	628.3	649.8	669.6	681.4	691.7
M02018	170.4	177.5	224.8	278.2	326.8	351.1	381.4	400.2	423.1	441.8	462.3	471.5	492.1	499.9	510.1
M02019	166.0	171.3	216.4	273.1	326.2	369.1	405.8	434.5	459.8	488.2	511.2	529.5	549.5	564.0	573.7
M02020	176.1	183.8	229.4	298.5	356.3	414.7	464.8	503.9	542.4	570.3	596.0	622.4	649.6	667.2	682.8
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	175.6	183.7	235.5	297.9	355.4	400.7	442.5	475.2	503.4	520.1	539.3	559.5	579.3	595.2	603.0
S.D.	7.9	9.5	15.2	21.1	28.3	35.8	42.5	48.3	51.5	51.5	52.4	57.2	57.6	59.6	58.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	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 2 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of males

Medium dose (BEA 100 mg/kg)

Male No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	90
M03021	176.5	187.7	239.2	301.6	356.8	399.0	430.8	455.4	475.0	501.9	522.4	549.7	564.8	581.7	584.0
M03022	185.2	192.2	245.6	314.7	365.7	414.9	451.1	490.8	516.0	542.8	561.7	578.0	595.1	610.9	611.2
M03023	176.1	184.2	235.2	309.4	381.8	443.8	490.5	535.9	572.0	609.6	617.7	637.6	661.5	671.2	672.8
M03024	160.8	167.3	207.7	258.4	309.0	342.5	376.4	402.3	424.5	446.7	467.6	484.7	507.3	523.2	523.1
M03025	174.0	179.8	233.3	298.6	356.6	397.7	429.9	461.4	485.3	500.8	512.1	532.2	552.2	550.7	553.6
M03026	181.2	192.0	255.4	325.4	380.6	432.3	485.5	525.5	552.2	585.8	607.9	640.0	658.1	673.7	685.4
M03027	178.0	186.1	223.9	271.7	316.7	344.6	372.2	399.5	422.4	444.7	461.3	477.1	493.4	503.0	513.7
M03028	167.8	173.2	214.3	263.8	299.2	328.9	355.6	374.7	407.8	437.4	456.7	473.9	488.9	499.1	516.7
M03029	177.5	186.7	240.3	302.2	371.6	420.8	468.1	499.8	528.4	550.6	572.0	597.3	622.7	636.9	651.1
M03030	171.3	179.5	226.9	282.1	340.9	387.5	426.0	451.0	488.8	506.2	522.9	549.1	570.7	583.2	598.2
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	174.8	182.9	232.2	292.8	347.9	391.2	428.6	459.6	487.2	512.7	530.2	552.0	571.5	583.4	591.0
S.D.	6.9	8.0	14.4	22.6	30.1	40.0	47.6	54.7	56.3	59.7	58.6	61.9	63.5	64.8	64.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	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 2 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of males

High dose (BEA 500 mg/kg)

Male No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	90
M04031	171.7	174.1	225.1	288.0	338.2	373.6	411.3	439.3	460.3	475.7	486.0	503.7	515.9	522.0	523.0
M04032	189.2	194.7	247.7	310.6	366.4	407.9	413.3	442.4	470.7	497.9	512.5	527.2	544.2	553.7	552.2
M04033	166.4	167.0	210.5	273.5	335.2	375.5	414.7	443.4	458.7	481.9	493.7	512.8	521.3	534.1	536.1
M04034	182.8	189.0	250.2	309.4	364.4	408.8	445.7	483.0	513.7	534.9	559.3	575.1	586.9	597.3	601.7
M04035	180.6	186.0	239.5	298.5	350.0	377.7	411.2	446.6	471.4	494.7	512.4	531.8	553.9	567.8	569.4
M04036	183.6	186.8	238.6	292.7	344.0	391.2	419.3	452.6	479.7	494.3	515.2	(Died)			
M04037	168.0	172.4	223.5	276.6	322.5	358.4	395.1	424.8	459.2	474.4	495.3	522.5	537.4	551.0	560.5
M04038	175.4	176.1	229.5	298.2	351.3	395.6	435.4	466.5	497.1	517.6	545.0	559.5	576.6	575.0	585.5
M04039	161.8	166.4	213.9	272.4	322.9	367.2	407.2	439.9	463.0	484.9	503.7	522.1	537.4	549.2	554.0
M04040	173.1	179.4	225.5	274.4	321.0	357.9	389.0	416.4	433.4	443.9	454.7	467.0	478.9	487.8	493.3
Number of males	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9
Mean	175.3	179.2	230.4	289.4	341.6	381.4	414.2	445.5	470.7	490.0	507.8	524.6	539.2	548.7	552.9
S.D.	8.7	9.6	13.4	14.7	16.7	18.7	16.8	19.0	22.3	24.8	29.4	31.1	32.4	31.8	32.6
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	KW	AN	AN	AN	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 2 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of females

Control (vehicle: corn oil)

Female No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	91
F01041	130.9	134.8	169.3	198.0	224.0	252.8	260.1	278.2	291.1	304.7	320.4	315.6	326.4	326.0	330.9
F01042	123.3	125.6	142.9	155.6	165.1	176.6	187.3	183.0	197.9	208.5	208.0	222.3	236.3	234.2	237.4
F01043	134.2	139.9	161.5	178.7	195.9	215.5	232.7	251.7	260.8	279.3	285.3	294.4	294.8	295.7	297.4
F01044	132.3	138.9	164.5	186.7	211.9	227.5	239.9	247.7	258.6	269.8	272.9	275.4	284.7	288.0	284.5
F01045	135.9	138.4	156.3	169.0	191.9	208.8	219.6	225.4	239.2	244.4	255.8	259.4	266.8	267.3	267.8
F01046	135.5	144.2	160.1	176.5	189.9	212.0	226.5	240.2	248.2	266.2	277.7	285.2	293.7	307.0	309.5
F01047	133.5	141.2	169.6	192.7	214.4	234.5	238.4	257.4	274.4	289.8	289.9	299.3	306.5	308.7	314.8
F01048	128.2	136.6	169.8	187.7	214.5	228.3	248.5	258.3	267.5	271.0	278.4	286.3	290.9	286.4	295.5
F01049	141.1	145.5	174.2	191.3	206.4	217.0	230.0	246.2	254.2	258.4	274.4	286.6	297.1	295.8	299.3
F01050	121.3	124.5	145.0	151.2	168.7	185.8	197.2	199.3	210.7	226.2	228.8	234.5	247.1	251.2	252.3
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	131.6	137.0	161.3	178.7	198.3	215.9	228.0	238.7	250.3	261.8	269.2	275.9	284.4	286.0	288.9
S.D.	6.0	7.0	10.6	15.9	19.8	22.4	22.1	28.7	28.2	28.9	31.7	29.1	27.2	27.9	28.9

Appendix 2 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Body weight of females

Low dose (BEA 20 mg/kg)

Female No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	91
F02051	126.4	132.0	155.9	175.9	202.7	225.5	242.3	253.2	269.1	276.4	283.3	297.1	303.2	309.4	308.8
F02052	134.2	138.9	155.5	176.0	197.9	216.2	225.9	236.8	250.7	258.0	266.4	274.6	273.0	281.8	290.8
F02053	114.2	120.6	144.8	163.8	188.0	206.4	217.0	227.0	242.6	248.5	254.5	257.5	270.5	275.3	267.9
F02054	142.0	148.9	173.0	197.9	221.8	241.9	263.1	276.7	289.0	295.3	301.9	315.9	320.8	327.3	333.2
F02055	139.8	138.7	166.4	191.8	212.3	245.4	265.5	280.1	287.9	311.2	329.0	340.4	345.1	357.7	358.0
F02056	130.8	132.0	156.9	171.3	184.3	206.8	220.8	230.0	248.2	262.3	267.6	271.9	283.1	290.0	289.3
F02057	125.7	131.0	150.5	170.4	182.9	199.5	210.8	214.0	221.8	229.6	235.1	238.6	245.2	250.6	252.3
F02058	133.0	139.7	158.4	183.3	205.3	228.5	239.8	252.7	267.2	273.3	277.7	288.5	294.9	302.6	302.3
F02059	125.8	128.5	159.0	174.9	190.9	215.4	233.1	239.7	243.6	253.9	259.7	263.4	264.5	271.4	269.6
F02060	133.1	139.4	164.6	185.8	201.5	226.4	251.5	263.3	278.5	297.8	309.8	317.5	326.1	338.0	348.7
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	130.5	135.0	158.5	179.1	198.8	221.2	237.0	247.4	259.9	270.6	278.5	286.5	292.6	300.4	302.1
S.D.	8.0	7.8	8.0	10.5	12.6	15.2	18.9	21.7	22.0	25.2	28.2	31.4	31.3	33.2	35.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

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 2-butoxyethyl acetate in rats

Body weight of females

Medium dose (BEA 100 mg/kg)

Female No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	91
F03061	139.7	144.8	173.6	199.1	228.3	241.7	265.0	271.0	277.9	275.6	290.3	302.2	305.0	307.3	311.8
F03062	116.3	115.8	142.4	157.3	183.2	197.9	208.0	229.4	241.9	251.3	250.7	265.3	276.0	273.2	270.8
F03063	118.6	118.8	131.4	142.4	160.8	173.5	178.7	185.2	199.4	209.6	211.6	220.5	234.4	237.1	233.7
F03064	136.6	137.4	162.9	184.9	206.4	228.7	242.7	245.4	262.9	275.6	280.7	282.3	290.0	293.4	286.4
F03065	125.7	134.3	157.0	183.5	202.5	218.0	236.3	249.1	257.3	259.4	270.9	278.0	283.2	285.5	288.1
F03066	134.7	141.4	154.9	182.8	206.3	226.6	239.3	260.0	270.8	282.2	292.6	309.0	319.9	322.9	327.5
F03067	133.0	134.7	171.6	202.1	212.7	242.8	250.6	264.4	277.5	277.5	290.4	298.7	303.5	310.5	313.8
F03068	133.4	140.5	165.7	185.7	205.5	220.0	236.9	245.3	253.8	265.0	269.5	278.4	281.3	286.3	292.8
F03069	138.5	143.2	172.6	194.0	218.5	241.7	258.2	272.6	289.8	297.0	328.2	343.4	348.5	348.3	350.3
F03070	134.8	136.4	165.3	179.7	191.5	201.3	207.8	220.0	232.6	247.7	248.1	258.1	272.8	281.4	283.2
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	131.1	134.7	159.7	181.2	201.6	219.2	232.4	244.2	256.4	264.1	273.3	283.6	291.5	294.6	295.8
S.D.	8.2	9.8	13.8	18.4	19.1	22.6	26.5	26.9	26.5	24.2	31.6	33.0	30.6	30.2	32.2
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

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 2-butoxyethyl acetate in rats

Body weight of females

High dose (BEA 500 mg/kg)

Female No.	Days of administration														
	1	2	8	15	22	29	36	43	50	57	64	71	78	85	91
F04071	136.1	136.8	156.6	173.0	192.7	214.0	216.9	240.4	251.3	259.3	262.7	275.5	287.3	289.4	286.0
F04072	135.2	139.4	163.6	188.2	210.6	230.3	259.7	274.2	286.8	289.5	301.1	316.0	317.2	315.9	321.1
F04073	137.1	135.1	161.7	183.5	211.8	235.4	248.5	257.7	279.1	288.1	308.0	317.5	327.1	336.0	333.3
F04074	120.9	121.9	143.2	161.8	190.2	209.6	222.9	226.9	237.7	252.0	255.9	257.9	275.3	273.8	278.5
F04075	129.5	129.9	156.0	173.8	196.8	221.2	240.3	255.9	261.6	270.5	278.4	285.4	289.3	292.4	293.4
F04076	128.9	129.8	159.9	181.4	210.0	229.8	251.5	263.4	273.1	283.2	289.4	298.7	306.4	310.8	307.2
F04077	140.9	147.8	182.1	208.8	242.2	253.7	267.9	277.7	283.1	287.0	297.7	296.5	296.1	303.9	307.0
F04078	131.0	132.2	158.5	181.4	208.2	233.5	264.4	278.5	297.1	287.9	291.8	306.8	310.6	312.4	320.2
F04079	145.3	148.7	173.4	182.4	207.3	224.4	238.8	239.7	257.2	269.7	267.2	274.5	286.3	290.7	287.7
F04080	133.3	129.9	156.4	180.0	201.2	219.7	231.7	235.4	246.3	253.4	260.1	257.2	267.2	271.7	267.6
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	133.8	135.2	161.1	181.4	207.1	227.2	244.3	255.0	267.3	274.1	281.2	288.6	296.3	299.7	300.2
S.D.	6.8	8.4	10.5	12.1	14.6	12.5	17.3	18.7	19.4	15.1	18.8	22.1	18.9	19.9	21.0
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

NS: Not significantly different from the control group.

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

Appendix 3

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	22.7	24.1	26.9	24.9	27.3	26.5	25.0	24.8	23.4	26.0	23.2	19.6	19.1
M01002	23.1	24.8	25.9	26.6	25.2	26.1	28.2	30.5	27.9	28.2	24.2	23.5	24.8
M01003	22.3	24.5	22.8	25.0	26.2	25.5	22.1	23.1	23.4	23.2	22.4	22.8	20.6
M01004	22.3	22.1	26.6	25.4	25.8	25.5	25.2	24.5	26.3	23.1	24.6	23.5	19.7
M01005	20.3	21.6	22.1	18.9	24.6	23.7	19.4	24.4	24.1	23.2	23.4	22.0	19.7
M01006	21.3	22.8	24.7	25.9	27.1	25.3	24.3	27.5	24.3	22.3	21.3	21.6	18.6
M01007	20.8	22.9	21.2	25.1	25.5	24.9	25.1	22.5	24.4	22.7	23.7	21.6	18.0
M01008	23.3	23.7	26.9	27.2	26.4	26.8	26.3	23.6	28.4	26.7	24.7	24.7	25.4
M01009	24.2	28.1	27.9	32.3	26.9	30.1	29.0	27.6	31.1	27.2	29.9	30.7	28.9
M01010	26.0	29.3	32.2	32.6	23.9	29.6	28.2	29.8	28.1	28.4	31.4	22.1	28.0
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	22.6	24.4	25.7	26.4	25.9	26.4	25.3	25.8	26.1	25.1	24.9	23.2	22.3
S.D.	1.7	2.5	3.2	3.9	1.1	2.0	2.9	2.8	2.6	2.4	3.2	3.0	4.1

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of males

Low dose (BEA 20 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M02011	23.0	24.0	24.9	22.9	23.2	24.3	22.1	22.7	23.3	19.7	23.3	19.3	22.5
M02012	19.2	20.7	23.1	20.9	23.2	25.5	25.8	22.7	21.2	21.0	24.2	18.1	20.2
M02013	28.3	26.0	25.7	28.0	28.0	30.4	27.7	24.0	24.4	25.6	26.1	23.4	23.2
M02014	25.6	26.8	26.6	28.0	27.3	31.1	31.2	29.4	26.9	30.0	31.2	27.0	29.9
M02015	22.0	26.4	25.8	25.8	24.9	28.0	23.9	22.0	22.8	22.0	19.5	19.6	18.7
M02016	23.5	23.4	22.7	23.8	24.3	22.2	23.6	20.5	23.2	20.7	22.3	20.5	21.6
M02017	23.1	24.3	25.9	29.5	31.1	27.3	25.9	23.0	24.3	25.1	21.9	19.4	19.8
M02018	20.1	23.7	26.8	26.1	25.8	22.9	23.6	23.7	22.0	21.7	20.9	19.0	22.5
M02019	21.1	21.4	24.1	25.3	22.5	24.6	23.6	20.9	24.6	26.9	22.8	24.2	23.7
M02020	23.7	23.7	25.2	27.8	28.5	26.3	27.8	25.0	25.8	24.8	28.3	23.6	23.4
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	23.0	24.0	25.1	25.8	25.9	26.3	25.5	23.4	23.9	23.8	24.1	21.4	22.6
S.D.	2.6	2.0	1.4	2.7	2.8	3.0	2.7	2.5	1.7	3.3	3.6	2.9	3.1
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	KW	AN	AN	DU	DU	DU	AN	DT	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 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of males

Medium dose (BEA 100 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M03021	22.8	21.4	23.1	23.2	27.5	23.4	22.3	23.0	21.6	22.5	22.7	23.8	21.0
M03022	20.4	23.8	23.6	26.6	25.1	25.0	24.2	21.5	22.7	25.9	24.2	23.6	23.3
M03023	21.0	24.1	25.3	27.8	28.6	31.7	29.5	28.7	26.5	25.0	25.1	20.6	22.9
M03024	19.6	21.1	22.6	23.3	23.1	22.4	22.9	21.8	22.7	23.0	21.9	22.6	21.4
M03025	21.8	24.9	23.5	27.3	28.2	25.1	23.9	23.4	22.7	22.7	24.1	21.5	19.3
M03026	25.1	28.6	26.7	27.8	30.3	26.6	27.0	28.3	27.9	28.6	28.0	24.7	23.8
M03027	20.8	22.6	22.7	24.8	22.4	24.7	23.1	22.7	23.5	22.1	23.5	22.1	21.5
M03028	18.8	18.7	21.6	20.2	21.3	20.8	22.3	20.6	20.3	21.4	22.8	20.0	18.1
M03029	23.2	25.5	27.9	29.9	31.4	26.4	28.8	23.3	25.8	27.0	27.8	25.2	22.1
M03030	23.3	24.4	25.8	24.9	25.1	25.9	29.0	25.1	27.6	27.5	22.6	22.3	23.5
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	21.7	23.5	24.3	25.6	26.3	25.2	25.3	23.8	24.1	24.6	24.3	22.6	21.7
S.D.	1.9	2.7	2.0	2.9	3.4	2.9	2.9	2.7	2.6	2.6	2.1	1.7	1.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	KW	AN	AN	DU	DU	DU	AN	DT	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 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of males

High dose (BEA 500 mg/kg)

Male No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
M04031	18.9	25.7	27.6	28.4	33.4	34.3	24.6	30.8	28.8	32.4	21.7	34.5	25.8
M04032	19.6	24.8	28.4	24.9	27.3	22.1	21.7	23.1	24.6	28.3	27.9	25.2	21.7
M04033	14.0	22.1	21.7	26.8	26.8	28.3	25.2	26.3	26.9	26.5	24.6	23.7	23.1
M04034	21.1	29.0	29.0	30.8	30.9	28.6	30.7	33.6	32.6	30.8	30.6	30.9	27.3
M04035	18.8	25.6	28.1	23.6	27.4	23.9	28.1	26.6	28.9	28.1	24.7	24.8	25.6
M04036	18.2	23.1	28.2	25.1	24.6	23.1	24.3	25.4	28.2	25.0	(Died)		
M04037	18.3	21.0	21.7	21.8	26.1	23.5	29.0	25.0	27.7	28.4	26.0	27.2	25.4
M04038	14.3	24.3	26.4	29.3	27.0	27.2	25.6	25.0	29.0	27.8	24.1	21.5	22.0
M04039	17.6	20.0	22.2	22.7	27.6	27.0	23.7	28.0	25.1	30.2	25.8	34.3	27.2
M04040	18.8	20.7	25.0	23.1	24.3	23.6	24.3	22.4	24.8	24.8	24.5	20.5	21.7
Number of males	10	10	10	10	10	10	10	10	10	10	9	9	9
Mean	18.0	23.6	25.8	25.7	27.5	26.2	25.7	26.6	27.7	28.2	25.5	27.0	24.4
S.D.	2.2	2.8	3.0	3.1	2.7	3.7	2.7	3.4	2.4	2.4	2.5	5.2	2.3
Significance	**	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS
Statistical method	DU	AN	AN	AN	KW	AN	AN	DU	DU	DU	AN	DT	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 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	17.0	17.7	15.4	18.2	19.1	18.1	19.1	14.6	16.9	16.8	15.1	14.3	14.0
F01042	16.0	15.8	12.5	14.6	10.0	13.6	13.5	9.6	14.7	14.4	10.4	15.5	14.2
F01043	20.1	14.3	17.2	17.5	13.2	17.7	17.7	15.6	15.1	16.2	14.8	12.9	9.1
F01044	18.8	19.1	17.8	18.5	17.2	17.5	15.2	13.1	16.6	16.6	15.8	12.6	13.9
F01045	16.4	16.3	14.9	11.0	15.2	15.0	15.0	9.9	17.0	14.8	13.5	9.4	12.9
F01046	20.5	16.8	16.4	16.4	12.5	17.9	16.9	14.8	12.1	17.4	16.8	14.8	12.1
F01047	17.9	16.3	14.0	18.6	17.2	16.8	16.8	13.6	18.4	13.2	17.7	18.2	13.0
F01048	18.7	15.3	17.0	17.0	16.8	14.0	15.8	13.2	13.6	12.0	15.8	13.9	13.2
F01049	17.7	14.0	17.4	16.6	17.2	14.1	15.7	18.0	20.2	14.7	18.0	21.1	15.2
F01050	17.7	14.4	16.6	14.2	18.2	16.2	14.3	11.9	15.7	16.9	14.8	13.0	14.7
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	18.1	16.0	15.9	16.3	15.7	16.1	16.0	13.4	16.0	15.3	15.3	14.6	13.2
S.D.	1.5	1.6	1.7	2.4	2.9	1.8	1.7	2.5	2.3	1.8	2.2	3.2	1.7

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of females

Low dose (BEA 20 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F02051	16.5	17.6	17.7	15.7	19.3	19.0	17.8	14.0	18.1	16.0	15.6	16.2	17.3
F02052	16.7	15.7	13.3	15.9	13.8	13.0	15.9	14.2	15.3	11.8	12.5	11.5	14.4
F02053	14.9	15.5	16.9	15.1	18.4	17.8	16.2	14.6	15.2	16.7	15.6	10.9	16.5
F02054	18.9	14.0	18.5	17.9	19.5	16.3	17.0	16.3	15.6	13.7	16.2	15.9	14.4
F02055	16.1	18.0	19.4	20.9	19.2	22.8	19.4	18.7	17.8	20.3	17.3	18.4	16.8
F02056	15.9	17.1	17.0	13.1	17.5	16.3	15.6	13.3	16.0	16.8	15.3	13.6	15.7
F02057	18.3	13.9	14.6	15.1	13.5	12.0	11.6	11.2	11.6	11.1	10.6	8.4	11.7
F02058	18.0	14.1	15.6	13.4	18.7	16.7	14.3	16.3	18.6	16.1	11.9	18.0	16.7
F02059	15.2	17.3	18.3	15.0	14.4	15.5	16.3	14.6	10.0	15.6	16.6	11.7	10.3
F02060	17.7	15.9	18.3	19.0	13.4	18.9	21.2	18.3	15.7	18.5	20.0	18.1	14.5
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	16.8	15.9	17.0	16.1	16.8	16.8	16.5	15.2	15.4	15.7	15.2	14.3	14.8
S.D.	1.4	1.6	1.9	2.5	2.6	3.1	2.6	2.3	2.7	2.8	2.8	3.5	2.3
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DU	DT	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).

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of females

Medium dose (BEA 100 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F03061	16.8	15.5	17.0	16.0	17.9	18.9	18.0	13.4	14.2	15.1	17.8	15.0	12.1
F03062	14.0	16.0	16.1	13.6	17.0	16.1	10.7	17.9	18.3	14.9	12.2	18.2	14.7
F03063	13.7	13.1	16.1	10.6	14.2	15.2	11.9	11.2	17.2	14.9	12.5	11.1	13.9
F03064	14.6	16.6	15.7	13.8	16.3	16.0	19.2	17.1	18.5	16.0	18.3	13.2	19.5
F03065	18.6	14.4	18.3	19.9	19.5	14.6	18.3	17.4	18.1	13.1	18.5	18.1	13.6
F03066	17.5	17.7	15.2	16.1	17.4	18.2	15.5	16.8	20.0	17.9	14.1	18.1	17.5
F03067	14.0	19.3	15.8	16.3	17.8	14.9	17.5	17.5	17.0	17.2	13.9	17.0	14.3
F03068	17.7	15.1	18.3	17.1	16.9	18.1	18.0	16.5	14.9	15.4	18.7	17.1	15.0
F03069	17.4	19.4	19.2	14.2	18.8	20.6	17.8	17.8	17.7	20.3	16.7	15.3	14.5
F03070	16.1	17.7	14.8	16.6	14.8	15.5	13.7	19.5	16.9	16.6	17.6	19.0	16.7
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	16.0	16.5	16.7	15.4	17.1	16.8	16.1	16.5	17.3	16.1	16.0	16.2	15.2
S.D.	1.8	2.1	1.5	2.5	1.6	2.0	3.0	2.4	1.7	2.0	2.6	2.5	2.1
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DT	DU	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).

Appendix 3 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Food consumption of females

High dose (BEA 500 mg/kg)

Female No.	Days of administration												
	1	8	15	22	29	36	43	50	57	64	71	78	85
F04071	12.8	16.7	15.9	18.9	20.6	21.8	16.4	20.0	22.5	18.4	15.4	18.4	15.5
F04072	16.6	15.2	18.2	22.3	21.4	16.8	23.2	22.9	20.4	19.9	24.0	22.9	17.8
F04073	14.3	18.2	20.6	19.0	22.9	23.6	21.1	18.9	24.6	23.7	22.0	19.5	22.5
F04074	13.1	16.5	18.0	13.9	18.4	18.4	16.1	13.8	18.9	19.3	18.1	16.9	19.5
F04075	12.2	16.0	16.9	18.5	18.5	17.9	19.8	18.0	19.0	20.2	20.6	18.6	16.5
F04076	13.0	16.9	16.6	22.7	20.2	17.3	24.5	18.8	19.0	21.4	21.5	20.7	17.9
F04077	19.8	16.4	18.7	20.9	28.8	18.0	23.6	29.3	24.6	20.9	35.0	24.3	20.7
F04078	18.7	17.9	16.7	18.4	22.8	19.9	23.1	21.9	21.4	19.1	19.1	18.5	17.3
F04079	17.1	17.5	20.4	16.9	24.4	21.7	22.6	15.4	21.2	28.0	21.9	17.9	20.8
F04080	12.2	16.4	17.7	15.4	19.2	16.9	19.8	15.6	20.4	19.1	23.0	15.7	13.3
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	15.0	16.8	18.0	18.7	21.7	19.2	21.0	19.5	21.2	21.0	22.1	19.3	18.2
S.D.	2.8	0.9	1.6	2.8	3.2	2.4	3.0	4.5	2.1	2.9	5.2	2.6	2.8
Significance	**	NS	NS	NS	**	*	**	**	**	**	**	**	**
Statistical method	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DT	DU	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).

Appendix 4

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Ophthalmologic examination of males

Findings	Group	Control (vehicle: corn oil)										Medium dose (BEA 100 mg/kg)										High dose (BEA 500 mg/kg)									
		Male No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M01 008	M01 009	M01 010	M03 021	M03 022	M03 023	M03 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M04 031	M04 032	M04 033	M04 034	M04 035	M04 037	M04 038	M04 039	M04 040
Cornea																															
Band-shaped opacity		-	-	RL	-	-	RL	RL	-	-	-	RL	-	RL	RL	RL	RL	-	-	RL	RL		RL	RL	RL	RL	-	-	-	-	-
Vitreous																															
Persistent hyaloid artery		-	-	-	-	-	-	-	-	-	-	-	-	-	L	-	-	L	-	RL		-	-	-	-	-	-	-	-	-	
Fundus																															
Scattered brown spots area		-	L	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-
Band-shaped hyper reflection		-	-	-	-	-	-	-	-	-	-	-	L	-	-	-	-	-	-	-		-	-	-	-	RL	-	-	-	R	

-, 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 2-butoxyethyl acetate 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	7.0	+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M01002	≥9.0	2+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M01003	6.5	2+	-	+	-	-	2+	light yellow	-	-	-	-	±	-
M01004	8.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M01005	8.0	2+	-	+	-	-	2+	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

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	21.5	1.040	86.7	188.19	121.4	1.86	4.05	2.61
M01002	12.5	1.059	75.8	242.16	130.6	0.95	3.03	1.63
M01003	10.4	1.074	118.7	292.11	189.9	1.23	3.04	1.97
M01004	12.4	1.063	110.0	254.67	174.6	1.36	3.16	2.17
M01005	5.5	1.079	103.3	248.95	121.5	0.57	1.37	0.67
Number of males	5	5	5	5	5	5	5	5
Mean	12.5	1.063	98.9	245.22	147.6	1.19	2.93	1.81
S.D.	5.8	0.015	17.4	37.30	32.3	0.48	0.97	0.73

S.G.: Specific gravity

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of males

Low dose (BEA 20 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	6.5	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
M02012	7.0	±	-	±	-	-	±	light yellow	-	-	-	-	±	-
M02013	8.0	2+	-	+	-	-	+	light yellow	-	-	-	-	±	-
M02014	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
M02015	8.0	+	-	±	-	-	±	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

Low dose (BEA 20 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	24.7	1.030	39.4	122.12	72.1	0.97	3.02	1.78
M02012	16.2	1.050	102.3	220.45	150.0	1.66	3.57	2.43
M02013	18.6	1.038	59.8	156.64	89.9	1.11	2.91	1.67
M02014	41.4	1.018	38.3	82.95	49.4	1.59	3.43	2.05
M02015	14.8	1.050	125.2	223.11	167.1	1.85	3.30	2.47
Number of males	5	5	5	5	5	5	5	5
Mean	23.1	1.037	73.0	161.05	105.7	1.44	3.25	2.08
S.D.	10.9	0.014	39.0	61.27	50.7	0.38	0.28	0.37
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

NS: Not significantly different from the control group.

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

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of males

Medium dose (BEA 100 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	7.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
M03022	6.5	2+	-	+	-	-	+	light yellow	+	-	-	-	±	-
M03023	7.5	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
M03024	6.5	2+	-	+	-	-	2+	light yellow	+	-	-	-	±	-
M03025	8.5	2+	-	+	-	-	+	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

Medium dose (BEA 100 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	11.7	1.070	165.0	317.22	199.4	1.93	3.71	2.33
M03022	20.4	1.038	95.9	153.20	116.2	1.96	3.13	2.37
M03023	13.6	1.053	122.8	232.69	154.0	1.67	3.16	2.09
M03024	13.9	1.048	96.9	173.00	114.3	1.35	2.40	1.59
M03025	9.5	1.063	109.9	249.23	161.9	1.04	2.37	1.54
Number of males	5	5	5	5	5	5	5	5
Mean	13.8	1.054	118.1	225.07	149.2	1.59	2.95	1.98
S.D.	4.1	0.013	28.4	65.21	35.4	0.39	0.57	0.40
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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).

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of males

High dose (BEA 500 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	7.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04032	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M04033	7.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
M04034	8.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
M04035	6.5	+	-	±	-	-	±	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													

High dose (BEA 500 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	43.6	1.024	43.4	89.07	55.4	1.89	3.88	2.42
M04032	11.5	1.069	108.6	238.38	114.4	1.25	2.74	1.32
M04033	20.5	1.050	99.2	182.98	133.7	2.03	3.75	2.74
M04034	21.1	1.058	120.4	217.00	148.0	2.54	4.58	3.12
M04035	19.3	1.055	110.0	206.54	132.9	2.12	3.99	2.56
Number of males	5	5	5	5	5	5	5	5
Mean	23.2	1.051	96.3	186.79	116.9	1.97	3.79	2.43
S.D.	12.0	0.017	30.5	58.15	36.4	0.47	0.67	0.67
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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).

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	6.5	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F01042	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	-	-
F01043	6.0	+	-	±	-	-	+	yellow	-	-	-	-	±	-
F01044	7.5	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F01045	6.5	±	-	±	-	-	±	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

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	10.0	1.055	128.9	269.84	188.9	1.29	2.70	1.89
F01042	7.9	1.035	40.3	78.68	40.2	0.32	0.62	0.32
F01043	6.5	1.064	139.0	293.54	204.0	0.90	1.91	1.33
F01044	4.5	1.077	193.8	259.33	203.1	0.87	1.17	0.91
F01045	5.9	1.058	130.8	208.77	136.8	0.77	1.23	0.81
Number of females	5	5	5	5	5	5	5	5
Mean	7.0	1.058	126.6	222.03	154.6	0.83	1.53	1.05
S.D.	2.1	0.015	55.1	85.90	69.6	0.35	0.80	0.59

S.G.: Specific gravity

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of females

Low dose (BEA 20 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	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F02052	7.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	±
F02053	6.5	+	-	±	-	-	±	light yellow	-	-	-	-	-	-
F02054	8.0	+	-	±	-	-	+	light yellow	-	-	-	-	±	-
F02055	6.5	+	-	±	-	-	+	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

Low dose (BEA 20 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	8.0	1.069	174.9	341.42	221.3	1.40	2.73	1.77
F02052	10.1	1.064	110.0	322.04	190.7	1.11	3.25	1.93
F02053	6.0	1.073	148.4	315.36	184.9	0.89	1.89	1.11
F02054	9.7	1.055	116.5	245.24	163.2	1.13	2.38	1.58
F02055	6.2	1.058	113.4	146.98	112.7	0.70	0.91	0.70
Number of females	5	5	5	5	5	5	5	5
Mean	8.0	1.064	132.6	274.21	174.6	1.05	2.23	1.42
S.D.	1.9	0.007	28.2	79.88	40.3	0.26	0.89	0.51
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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

NS: Not significantly different from the control group.

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

DT: Analysis by Dunnett type mean rank test.

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of females

Medium dose (BEA 100 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	6.0	±	-	±	-	-	±	light yellow	-	-	-	-	-	-
F03062	8.5	+	-	±	-	-	±	light yellow	-	-	-	-	±	-
F03063	6.5	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F03064	6.0	+	-	+	-	-	2+	light yellow	-	-	-	-	±	-
F03065	6.0	+	-	±	-	-	+	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

Medium dose (BEA 100 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
F03061	14.0	1.041	95.3	177.49	137.5	1.33	2.48	1.93
F03062	7.3	1.037	79.8	89.57	57.6	0.58	0.65	0.42
F03063	22.8	1.024	61.4	105.00	69.0	1.40	2.39	1.57
F03064	7.6	1.042	97.4	103.10	77.3	0.74	0.78	0.59
F03065	6.3	1.075	131.4	290.35	231.0	0.83	1.83	1.46
Number of females	5	5	5	5	5	5	5	5
Mean	11.6	1.044	93.1	153.10	114.5	0.98	1.63	1.19
S.D.	7.0	0.019	25.8	84.09	72.1	0.37	0.87	0.66
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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

NS: Not significantly different from the control group.

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

DT: Analysis by Dunnett type mean rank test.

Appendix 5 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Urinalysis of females

High dose (BEA 500 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
F04071	7.5	±	-	-	-	-	±	light yellow	+	-	-	-	±	-
F04072	7.0	-	-	-	-	-	±	light yellow	-	-	-	-	-	-
F04073	8.0	±	-	-	-	-	±	light yellow	-	-	-	-	±	-
F04074	7.0	+	-	-	-	-	±	light yellow	-	-	-	-	±	-
F04075	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

High dose (BEA 500 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
F04071	18.2	1.040	80.6	165.25	107.9	1.47	3.01	1.96
F04072	45.3	1.011	11.3	25.28	5.3	0.51	1.15	0.24
F04073	12.9	1.065	101.8	246.23	159.4	1.31	3.18	2.06
F04074	16.1	1.047	106.1	206.93	148.7	1.71	3.33	2.39
F04075	39.3	1.015	26.6	37.45	24.6	1.05	1.47	0.97
Number of females	5	5	5	5	5	5	5	5
Mean	26.4	1.036	65.3	136.23	89.2	1.21	2.43	1.52
S.D.	14.8	0.023	43.7	100.01	70.8	0.46	1.03	0.89
Significance	**	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	AN	AN	AN	AN	AN	AN

S.G.: Specific gravity

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

NS: Not significantly different from the control group.

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

DT: Analysis by Dunnett type mean rank test.

Appendix 6

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	812	14.6	44.0	54.2	18.0	33.2	96.6	17.9	15.3	99.2	12.8	1.4	0.1	3.0	82.7	2.39
M01002	764	14.2	43.3	56.7	18.6	32.8	81.4	15.6	16.4	68.9	14.7	0.6	0.1	3.2	81.4	4.09
M01003	809	14.2	43.7	54.0	17.6	32.5	93.0	15.2	13.3	66.2	13.5	1.4	0.2	3.2	81.7	3.32
M01004	792	13.7	41.1	51.9	17.3	33.3	124.7	16.4	22.3	64.3	16.7	1.4	0.0	4.0	77.9	3.40
M01005	848	15.3	47.0	55.4	18.0	32.6	74.6	16.9	16.2	49.5	26.9	1.2	0.0	2.8	69.1	3.08
M01006	837	14.3	43.1	51.5	17.1	33.2	97.4	18.4	19.7	86.7	24.5	1.2	0.0	4.7	69.6	2.60
M01007	760	13.5	41.0	53.9	17.8	32.9	99.3	15.1	15.7	53.7	30.4	0.7	0.0	3.5	65.4	3.23
M01008	850	15.3	45.9	54.0	18.0	33.3	109.5	17.0	13.5	125.7	15.3	1.4	0.0	3.4	79.9	3.04
M01009	889	14.4	43.3	48.7	16.2	33.3	114.1	16.1	21.0	100.5	18.5	1.4	0.1	4.1	75.9	2.86
M01010	802	14.3	43.3	54.0	17.8	33.0	81.8	16.7	16.0	59.2	17.5	1.9	0.0	6.8	73.8	3.40
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	816	14.4	43.6	53.4	17.6	33.0	97.2	16.5	16.9	77.4	19.1	1.3	0.1	3.9	75.7	3.14
S.D.	40	0.6	1.8	2.2	0.7	0.3	15.7	1.1	3.1	24.7	6.1	0.4	0.1	1.2	6.1	0.47

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Hematological analysis of males

Low dose (BEA 20 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	774	13.7	41.5	53.6	17.7	33.0	84.2	16.8	14.9	51.6	20.9	1.2	0.0	3.7	74.2	2.83
M02012	790	13.1	40.0	50.6	16.6	32.8	104.8	13.3	10.4	84.7	15.8	1.4	0.0	3.1	79.7	3.40
M02013	758	13.7	42.1	55.5	18.1	32.5	99.5	16.1	15.3	72.7	16.2	1.2	0.0	3.9	78.7	2.58
M02014	841	14.0	42.5	50.5	16.6	32.9	93.3	13.1	12.8	46.2	20.1	0.9	0.0	4.8	74.2	2.86
M02015	780	13.5	41.6	53.3	17.3	32.5	94.4	14.5	13.0	52.4	15.7	1.1	0.0	4.0	79.2	3.15
M02016	766	14.0	41.7	54.4	18.3	33.6	118.1	14.7	17.8	68.1	19.7	1.3	0.0	4.1	74.9	3.69
M02017	787	13.7	42.1	53.5	17.4	32.5	92.3	14.7	17.2	85.2	14.5	1.1	0.1	3.4	80.9	3.59
M02018	865	14.9	45.5	52.6	17.2	32.7	89.9	21.4	19.7	58.9	20.8	1.5	0.0	3.7	74.0	2.60
M02019	875	14.9	46.5	53.1	17.0	32.0	112.3	18.4	13.1	119.7	12.4	1.3	0.1	4.9	81.3	2.90
M02020	811	13.9	42.5	52.4	17.1	32.7	110.9	16.7	20.1	96.6	19.1	2.3	0.0	4.3	74.3	3.12
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	805	13.9	42.6	53.0	17.3	32.7	100.0	16.0	15.4	73.6	17.5	1.3	0.0	4.0	77.1	3.07
S.D.	42	0.6	1.9	1.5	0.6	0.4	11.1	2.5	3.2	23.2	3.0	0.4	0.0	0.6	3.1	0.39
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DT	AN	DT	AN	KW	DU	DT	AN	AN	DU	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

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

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Hematological analysis of males

Medium dose (BEA 100 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	750	13.2	40.7	54.3	17.6	32.4	109.4	16.2	16.4	103.7	9.5	0.8	0.1	1.4	88.2	2.96
M03022	735	13.3	40.8	55.5	18.1	32.6	82.8	14.9	16.7 §	57.4	21.1	1.4	0.0	4.2	73.3	3.16
M03023	651	13.1	42.2	64.8	20.1	31.0	92.6	12.4	13.1	55.1	8.0	0.9	0.0	3.8	87.3	6.54
M03024	791	14.1	42.7	54.0	17.8	33.0	93.5	16.3	16.1	63.7	23.8	2.5	0.0	4.9	68.8	3.48
M03025	803	13.8	42.8	53.3	17.2	32.2	108.3	14.7	13.7	42.8	22.7	1.9	0.0	3.7	71.7	4.11
M03026	833	14.9	46.5	55.8	17.9	32.0	103.0	15.2	15.7	57.3	16.4	0.7	0.0	3.7	79.2	4.17
M03027	758	13.0	41.0	54.1	17.2	31.7	103.6	15.5	12.0	69.1	15.5	0.9	0.0	2.7	80.9	4.81
M03028	791	14.1	43.6	55.1	17.8	32.3	104.6	16.3	17.8	63.2	14.4	0.8	0.0	3.2	81.6	3.35
M03029	685	12.0	36.9	53.9	17.5	32.5	100.4	18.2	19.9	145.3	11.9	1.7	0.1	3.4	82.9	4.45
M03030	835	14.4	42.7	51.1	17.2	33.7	94.5	15.0	18.4	54.1	21.6	1.7	0.0	3.1	73.6	3.04
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	763	13.6	42.0	55.2	17.8	32.3	99.3	15.5	16.0	71.2	16.5	1.3	0.0	3.4	78.8	4.01
S.D.	60	0.8	2.5	3.6	0.9	0.7	8.3	1.5	2.5	30.6	5.6	0.6	0.0	0.9	6.6	1.09
Significance	*	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DT	AN	DT	AN	KW	DU	DT	AN	AN	DU	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

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

§: Remeasurement was performed because the first measurement value deviated from the control criteria for laboratory error. The remeasurement value was adopted.

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Hematological analysis of males

High dose (BEA 500 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	490	10.0	35.5	72.4	20.4	28.2	92.4	14.8	16.0	59.7	19.1	0.0	0.0	2.5	78.4	17.49
M04032	455	10.0	34.2	75.2	22.0	29.2	78.2	13.6	15.3	63.5	6.8	0.2	0.0	1.3	91.7	16.08
M04033	512	11.0	37.7	73.6	21.5	29.2	94.4	12.3	8.5 ^b	54.3	19.7	0.0	0.0	6.1	74.2	12.80
M04034	482	10.1	37.2	77.2	21.0	27.2	89.3	13.7	15.9	53.5	6.5	0.0	0.0	1.9	91.6	24.46
M04035	472	9.9	34.9	73.9	21.0	28.4	94.1	13.3	15.1	56.2	7.6	0.0	0.0	2.7	89.7	14.54
M04037	505	10.1	34.6	68.5	20.0	29.2	84.5	14.7	18.1	47.7	15.5	0.0	0.0	3.4	81.1	13.89
M04038	537	11.4	39.2	73.0	21.2	29.1	85.1	12.2	9.0 ^b	75.7	13.2	0.0	0.0	3.4	83.4	14.01
M04039	568	11.1	38.0	66.9	19.5	29.2	104.5	13.8	16.8	57.5	9.6	0.0	0.0	1.7	88.7	12.51
M04040	535	11.5	39.2	73.3	21.5	29.3	80.7	12.9	15.0	53.8	10.3	0.0	0.0	2.2	87.5	11.67
Number of males	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	506	10.6	36.7	72.7	20.9	28.8	89.2	13.5	14.4	58.0	12.0	0.0	0.0	2.8	85.1	15.27
S.D.	36	0.7	2.0	3.2	0.8	0.7	8.1	0.9	3.4	8.0	5.1	0.1	0.0	1.4	6.2	3.88
Significance	**	**	**	**	**	**	NS	**	NS	NS	*	**	NS	NS	**	**
Statistical method	DU	DU	DU	DU	DU	DT	AN	DT	AN	KW	DU	DT	AN	AN	DU	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

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

b: Remeasurement was performed because a change point of the reaction was not detected between the reagent and the sample. The remeasurement value was adopted.

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	733	13.7	41.2	56.2	18.7	33.3	98.8	13.1	9.3	84.4	7.2	1.5	0.1	2.1	89.1	3.32
F01042	706	12.9	38.7	54.8	18.3	33.3	80.0	12.6	13.2	26.7	10.2	2.2	0.0	2.6	85.0	3.77
F01043	738	13.9	41.0	55.6	18.8	33.9	104.7	11.7	12.2	51.5	11.3	2.5	0.0	3.1	83.1	2.31
F01044	729	13.4	39.5	54.2	18.4	33.9	104.0	11.9	11.9	38.4	10.9	1.6	0.0	1.6	85.9	2.14
F01045	774	14.4	42.9	55.4	18.6	33.6	94.3	11.4	13.6	37.2	13.2	2.4	0.0	4.0	80.4	2.90
F01046	763	13.6	40.3	52.8	17.8	33.7	87.1	11.3	11.9	57.6	19.6	1.0	0.0	4.2	75.2	2.78
F01047	715	13.6	41.2	57.6	19.0	33.0	88.4	12.3	10.1	67.7	5.3	1.2	0.0	1.6	91.9	2.59
F01048	715	13.3	39.6	55.4	18.6	33.6	84.3	11.2	8.8	36.1	14.7	1.4	0.0	3.0	80.9	2.80
F01049	749	14.4	43.2	57.7	19.2	33.3	90.9	11.9	11.5	66.0	10.4	1.5	0.0	4.8	83.3	2.64
F01050	794	14.6	43.3	54.5	18.4	33.7	101.5	11.5	8.8	56.7	8.1	1.1	0.0	2.6	88.2	2.21
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	742	13.8	41.1	55.4	18.6	33.5	93.4	11.9	11.1	52.2	11.1	1.6	0.0	3.0	84.3	2.75
S.D.	28	0.5	1.6	1.5	0.4	0.3	8.6	0.6	1.8	17.8	4.1	0.5	0.0	1.1	4.8	0.50

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Hematological analysis of females

Low dose (BEA 20 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	696	13.5	41.5	59.6	19.4	32.5	89.1	12.2	8.6	43.1	17.4	1.4	0.0	3.0	78.2	3.82
F02052	728	12.9	39.5	54.3	17.7	32.7	96.4	12.1	10.1 ^b	42.5	12.5	1.4	0.2	4.0	81.9	3.04
F02053	691	13.4	41.1	59.5	19.4	32.6	80.4	11.7	11.4	37.3	13.4	3.2	0.0	3.5	79.9	2.85
F02054	746	13.3	40.6	54.4	17.8	32.8	84.7	11.3	11.7	49.7	23.2	1.6	0.0	2.4	72.8	2.57
F02055	742	13.5	40.4	54.4	18.2	33.4	94.3	11.2	10.3	48.1	11.4	2.1	0.0	3.1	83.4	2.25
F02056	718	13.1	39.2	54.6	18.2	33.4	108.3	11.4	14.1	68.6	11.4	0.6	0.1	2.0	85.9	2.35
F02057	731	13.2	39.3	53.8	18.1	33.6	94.2	11.7	11.3	42.0	11.7	1.4	0.0	2.6	84.3	2.16
F02058	686	12.8	38.8	56.6	18.7	33.0	96.5	11.7	13.8	55.4	24.0	0.7	0.0	2.9	72.4	3.15
F02059	769	14.0	41.9	54.5	18.2	33.4	86.0	11.2	9.8	38.8	11.2	1.5	0.0	4.6	82.7	2.44
F02060	725	13.9	42.7	58.9	19.2	32.6	90.6	11.7	9.8	52.3	15.9	1.3	0.0	4.0	78.8	2.85
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	723	13.4	40.5	56.1	18.5	33.0	92.1	11.6	11.1	47.8	15.2	1.5	0.0	3.2	80.0	2.75
S.D.	26	0.4	1.3	2.4	0.6	0.4	7.8	0.3	1.8	9.4	4.9	0.7	0.1	0.8	4.6	0.51
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DT	DU	DT	DU	DT	AN	AN	AN	DT	AN	AN	AN	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

^b: Remeasurement was performed because a change point of the reaction was not detected between the reagent and the sample. The remeasurement value was adopted.

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Hematological analysis of females

Medium dose (BEA 100 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	619	12.0	38.0	61.4	19.4	31.6	85.9	13.2	10.0	50.2	14.1	0.2	0.0	4.8	80.9	5.45
F03062	674	12.8	39.4	58.5	19.0	32.5	92.5	12.3	8.3	46.2	11.5	1.5	0.0	2.6	84.4	5.55
F03063	628	12.4	38.1	60.7	19.7	32.5	72.3	11.1	8.7 ^b	29.3	15.4	1.0	0.0	6.5	77.1	4.50
F03064	626	12.2	37.8	60.4	19.5	32.3	79.6	11.7	11.8	36.9	12.0	1.6	0.0	3.5	82.9	4.15
F03065	626	12.5	39.4	62.9	20.0	31.7	90.1	12.1	11.0	28.9	12.1	1.7	0.0	2.8	83.4	8.39
F03066	665	12.5	38.5	57.9	18.8	32.5	100.1	11.3	12.1	60.0	12.1	1.2	0.0	4.0	82.7	4.43
F03067	646	12.4	39.1	60.5	19.2	31.7	84.7	12.0	12.6	47.9	13.0	1.0	0.2	2.9	82.9	2.97
F03068	615	11.8	37.4	60.8	19.2	31.6	100.3	11.1	11.3	42.3	8.5	1.2	0.0	2.4	87.9	4.79
F03069	593	12.1	40.6	68.5	20.4	29.8	96.0	11.4	8.7	68.6	6.7	0.3	0.0	1.7	91.3	8.33
F03070	651	12.9	40.3	61.9	19.8	32.0	88.7	11.6	10.4	51.7	11.0	1.2	0.0	3.3	84.5	7.61
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	634	12.4	38.9	61.4	19.5	31.8	89.0	11.8	10.5	46.2	11.6	1.1	0.0	3.5	83.8	5.62
S.D.	25	0.3	1.1	2.9	0.5	0.8	8.9	0.6	1.5	12.6	2.5	0.5	0.1	1.4	3.8	1.87
Significance	**	**	**	*	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	DU	DU	DU	DT	DU	DT	DU	DT	AN	AN	AN	DT	AN	AN	AN	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

^b: Remeasurement was performed because a change point of the reaction was not detected between the reagent and the sample. The remeasurement value was adopted.

Appendix 6 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Hematological analysis of females

High dose (BEA 500 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 %
F04071	410 #	9.8	38.5	93.9	23.9	25.5	85.8	12.9	11.5	49.3	10.3	0.2	0.0	4.5	85.0	20.31
F04072	415 #	10.0	40.6	97.8	24.1	24.6	85.5	13.0	9.9	43.0	13.5	0.2	0.0	2.1	84.2	25.96 †
F04073	407 #	9.4 #	37.1	91.2	23.1	25.3	83.7	12.0	10.6	35.3	17.8	0.3	0.0	2.0	79.9	25.12 †
F04074	431 #	10.4	40.5	94.0	24.1	25.7	63.7	16.3	§	29.7	18.8	0.0	0.0	2.4	78.8	20.09
F04075	419 #	10.0	36.7	87.6	23.9	27.2	88.4	13.4	12.3	35.0	6.2	0.3	0.0	2.6	90.9	23.51 †
F04076	441	10.1	39.4	89.3	22.9	25.6	78.1	12.3	13.5	47.2	9.6	0.2	0.0	2.5	87.7	19.97
F04077	461	10.4	40.2	87.2	22.6	25.9	65.9	13.5	14.4	41.7	14.6	0.7	0.0	1.7	83.0	18.70
F04078	483	10.8	39.2	81.2	22.4	27.6	82.3	12.5	9.7	41.9	17.2	0.5	0.0	2.1	80.2	15.80
F04079	407 #	10.1	37.9	93.1	24.8	26.6	72.3	11.8	9.7	60.3	9.5	0.0	0.0	2.3	88.2	26.29 †
F04080	372 #	9.4 #	36.0	96.8	25.3	26.1	72.1	12.7	14.4	50.0	12.6	0.2	0.0	2.0	85.2	26.47 †
Number of females	10	10	10	10	10	10	10	10	9	10	10	10	10	10	10	10
Mean	425	10.0	38.6	91.2	23.7	26.0	77.8	13.0	11.8	43.3	13.0	0.3	0.0	2.4	84.3	22.22
S.D.	31	0.4	1.6	5.0	0.9	0.9	8.8	1.3	2.0	8.9	4.1	0.2	0.0	0.8	3.9	3.73
Significance	**	**	**	**	**	**	**	*	NS	NS	NS	**	NS	NS	NS	**
Statistical method	DU	DU	DU	DT	DU	DT	DU	DT	AN	AN	AN	DT	AN	AN	AN	DT

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

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

#: Remeasurement was performed because the first measurement value deviated from the control criteria for laboratory error. The first measurement value was adopted.

§: Coagulation reaction was undetected as results of remeasurements.

†: Remeasurement was performed because the first measurement value was out of linearity guarantee range. The first measurement value was adopted.

Appendix 7

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	CPK 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	5.3	3.3	1.65	138	37	60	52	28	0	130	9.5	0.29	0.05	326	5.4	9.0	146.0	3.85	106.9
M01002	5.9	3.7	1.68	140	43	97	94	39	0	814	10.9	0.34	0.05	407	5.8	9.2	144.9	3.86	105.9
M01003	5.5	3.6	1.89	151	48	88	54	24	0	150	10.7	0.37	0.06	501	5.1	9.3	145.0	3.97	106.8
M01004	5.8	3.6	1.64	116	62	96	60	30	0	123	9.4	0.27	0.04	303	5.1	9.5	145.9	3.95	107.3
M01005	4.8	3.3	2.20	125	39	32	50	24	0	493	14.2	0.34	0.04	465	6.7	8.7	146.0	4.04	110.6
M01006	5.4	3.4	1.70	134	48	62	49	26	0	116	12.4	0.31	0.05	318	6.1	9.3	143.9	3.98	105.1
M01007	5.6	3.5	1.67	161	58	40	82	35	0	626	12.4	0.36	0.06	291	6.6	9.0	143.9	3.98	105.3
M01008	5.5	3.4	1.62	148	41	67	72	56 #	0	384	12.6	0.28	0.04	408	6.2	9.1	145.3	3.78	105.2
M01009	5.6	3.5	1.67	178	56	76	59	25	0	216	12.3	0.25	0.06	624	5.7	9.1	143.9	3.64	104.6
M01010	5.4	3.5	1.84	132	44	62	62	23	0	640	9.5	0.32	0.06	382	5.8	9.1	145.4	3.71	105.0
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.5	3.5	1.76	142	48	68	63	31	0	369	11.4	0.31	0.05	403	5.9	9.1	145.0	3.88	106.3
S.D.	0.3	0.1	0.18	18	9	22	15	10	0	260	1.6	0.04	0.01	105	0.6	0.2	0.9	0.13	1.8

Remeasurement was performed because the first measurement value deviated from the control criteria for laboratory error. The first measurement value was adopted.

Appendix 7 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Blood biochemical analysis of males

Low dose (BEA 20 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	CPK 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	5.4	3.4	1.70	153	52	25	61	30	0	212	12.4	0.40	0.06	564	6.3	8.7	145.0	3.75	105.8
M02012	5.5	3.4	1.62	135	59	37	57	31	0	196	13.0	0.31	0.06	453	4.9	9.1	145.2	3.71	108.4
M02013	4.9	3.2	1.88	169	34	41	62	23	0	261	12.4	0.26	0.06	380	5.7	8.8	145.4	3.93	107.2
M02014	5.9	3.8	1.81	154	46	95	53	26	0	189	9.0	0.27	0.05	362	5.2	9.4	143.7	3.97	103.5
M02015	5.0	3.3	1.94	125	52	55	44	23	0	100	11.2	0.31	0.05	350	5.0	8.7	145.0	4.04	107.7
M02016	5.7	3.6	1.71	133	57	64	61	27	0	131	11.1	0.29	0.05	498	6.3	9.2	146.5	4.09	105.1
M02017	5.6	3.5	1.67	132	49	47	44	23	0	129	11.6	0.33	0.07	418	5.9	9.1	145.6	3.98	105.6
M02018	5.4	3.6	2.00	144	27	42	58	32	0	484	10.4	0.23	0.04	378	6.1	9.0	145.6	3.91	107.0
M02019	5.6	3.7	1.95	162	48	28	61	29	0	419	11.8	0.31	0.06	359	5.4	9.2	144.2	3.93	104.8
M02020	5.3	3.4	1.79	200	49	56	74	33	0	292	12.7	0.33	0.05	349	6.5	9.3	143.8	3.97	103.0
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.4	3.5	1.81	151	47	49	58	28	0	241	11.6	0.30	0.06	411	5.7	9.1	145.0	3.93	105.8
S.D.	0.3	0.2	0.13	22	10	20	9	4	0	126	1.2	0.05	0.01	73	0.6	0.2	0.9	0.12	1.8
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	DU	AN	DU	DT	DT	KW	DU	AN	AN	DU	DU	KW	DU	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 2-butoxyethyl acetate in rats

Blood biochemical analysis of males

Medium dose (BEA 100 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	CPK 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	5.7	3.5	1.59	156	44	51	56	29	0	188	11.9	0.40	0.04	976	6.6	9.0	144.7	4.14	106.7
M03022	5.3	3.3	1.65	125	41	39	60	28	0	197	10.6	0.35	0.05	496	5.6	8.8	143.9	4.00	104.3
M03023	5.6	3.7	1.95	138	75	72	50	24	0	250	9.8	0.32	0.04	345	5.5	9.1	144.3	4.27	105.9
M03024	5.4	3.4	1.70	124	45	36	76	39	0	130	11.9	0.33	0.05	661	5.9	9.0	144.0	4.33	105.7
M03025	5.2	3.5	2.06	166	53	33	51	27	0	117	11.5	0.39	0.04	381	5.3	8.7	144.2	3.91	107.9
M03026	5.5	3.4	1.62	142	52	48	53	27	0	207	12.2	0.33	0.03	368	7.3	9.1	145.2	4.08	104.9
M03027	4.8	3.1	1.82	145	34	18	52	26	0	82	9.3	0.25	0.03	422	6.3	8.7	144.5	3.87	105.6
M03028	5.3	3.4	1.79	150	55	118	49	21	0	504	12.7	0.29	0.02	512	6.9	9.4	144.8	3.96	104.2
M03029	5.1	3.4	2.00	157	35	55	56	23	0	223	11.6	0.33	0.04	325	6.6	8.8	144.0	4.21	105.2
M03030	5.5	3.3	1.50	135	63	24	61	25	0	758	10.6	0.30	0.04	452	6.3	9.1	145.6	4.03	106.0
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.3	3.4	1.77	144	50	49	56	27	0	266	11.2	0.33	0.04	494	6.2	9.0	144.5	4.08	105.6
S.D.	0.3	0.2	0.19	14	13	29	8	5	0	208	1.1	0.04	0.01	196	0.6	0.2	0.6	0.15	1.1
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	*	NS
Statistical method	AN	AN	DU	AN	DU	DT	DT	KW	AN	AN	AN	DU	DU	KW	DU	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 2-butoxyethyl acetate in rats

Blood biochemical analysis of males

High dose (BEA 500 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	CPK 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	5.3	3.7	2.31	142	36	42	77	34	0	477	9.3	0.41	0.05	369	7.0	9.0	146.6	4.26	106.8
M04032	5.2	3.5	2.06	128	34	34	58	27	0	121	10.8	0.31	0.04	469	5.7	8.6	143.7	4.07	107.0
M04033	4.9	3.4	2.27	114	40	38	67	36	0	254	11.8	0.38	0.03	552	6.5	8.6	145.1	4.22	108.5
M04034	4.9	3.4	2.27	137	38	41	68	33	0	323	16.3	0.42	0.05	470	7.5	8.6	144.7	4.38	107.1
M04035	5.2	3.4	1.89	129	25	31	64	31	0	248	12.0	0.39	0.05	481	7.6	8.6	144.8	4.33	107.7
M04037	5.2	3.4	1.89	131	27	39	60	25	0	167	11.3	0.29	0.03	610	6.0	8.6	145.1	3.72	107.6
M04038	5.1	3.5	2.19	145	31	48	64	34	0	316	10.4	0.31	0.05	384	7.3	9.1	144.1	3.85	103.9
M04039	5.6	3.7	1.95	143	40	40	65	29	0	116	13.8	0.40	0.04	706	7.2	9.1	145.0	4.38	104.8
M04040	5.3	3.7	2.31	125	35	21	68	36	0	405	12.8	0.35	0.05	398	6.5	8.7	145.1	3.90	106.0
Number of males	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	5.2	3.5	2.13	133	34	37	66	32	0	270	12.1	0.36	0.04	493	6.8	8.8	144.9	4.12	106.6
S.D.	0.2	0.1	0.18	10	5	8	5	4	0	124	2.1	0.05	0.01	112	0.7	0.2	0.8	0.25	1.5
Significance	NS	NS	**	NS	*	**	NS	NS	NS	NS	NS	NS	NS	NS	**	**	NS	**	NS
Statistical method	AN	AN	DU	AN	DU	DT	DT	KW	AN	AN	AN	DU	DU	KW	DU	DU	AN	DU	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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 2-butoxyethyl acetate 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	CPK 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	3.5	2.06	159	39	25	54	20	1	345	16.0	0.53	0.07	373	6.0	8.7	143.6	3.86	106.9
F01042	5.6	3.9	2.29	131	53	17	47	21	1	173	12.8	0.34	0.07	297	3.8	8.4	145.2	4.18	111.2
F01043	6.5	4.5	2.25	119	67	28	43	22	0	150	13.4	0.39	0.06	112	5.1	9.3	146.7	3.79	109.2
F01044	5.6	3.9	2.29	121	65	20	55	21	0	163	13.7	0.48	0.06	208	4.4	8.8	143.9	3.98	108.2
F01045	6.0	4.1	2.16	107	50	13	46	16	0	96	13.0	0.36	0.08	308	5.0	8.8	145.3	3.95	107.4
F01046	6.2	4.2	2.10	158	59	27	45	21	0	111	14.3	0.40	0.06	169	5.3	9.9	142.6	3.95	107.2
F01047	5.6	3.8	2.11	124	58	16	49	20	0	180	14.3	0.45	0.08	293	6.0	9.6	143.6	4.48	108.6
F01048	6.3	4.3	2.15	159	56	14	57	24	1	135	14.8	0.51	0.09	294	5.6	9.8	144.7	4.88	106.8
F01049	6.0	4.3	2.53	124	63	31	44	19	1	167	13.1	0.33	0.10	189	5.9	10.1	146.9	3.62	109.2
F01050	5.6	3.9	2.29	125	50	12	51	18	0	284	13.7	0.36	0.09	279	7.7	9.7	145.4	4.76	107.4
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.9	4.0	2.22	133	56	20	49	20	0	180	13.9	0.42	0.08	252	5.5	9.3	144.8	4.15	108.2
S.D.	0.4	0.3	0.14	19	8	7	5	2	1	77	1	0.07	0.01	79	1.1	0.6	1.4	0.42	1.4

Appendix 7 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Blood biochemical analysis of females

Low dose (BEA 20 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	CPK 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	5.8	3.7	1.76	136	62	38	63	27	1	473	13.5	0.42	0.05	484	5.8	9.3	144.4	4.63	109.2
F02052	5.5	3.8	2.24	127	44	20	58	19	1	861 #	11.5	0.44	0.07	215	5.1	8.8	145.8	4.12	109.6
F02053	6.0	3.9	1.86	110	50	20	65	27	1	178	14.7	0.42	0.05	234	4.9	9.2	147.5	4.08	111.6
F02054	6.5	4.4	2.10	126	77	54	40	20	0	125	15.1	0.38	0.06	179	4.0	9.4	146.2	3.99	109.5
F02055	5.7	3.9	2.17	136	60	74	46	16	1	158	13.7	0.35	0.07	259	5.5	9.1	145.3	3.73	108.9
F02056	5.8	4.0	2.22	123	66	26	47	19	1	281	13.6	0.39	0.04	286	5.5	9.1	144.3	4.09	109.6
F02057	6.0	4.1	2.16	135	59	33	49	22	0	571	12.7	0.35	0.07	190	6.4	10.0	145.7	4.77	107.1
F02058	6.5	4.4	2.10	139	63	25	51	22	1	178	12.0	0.35	0.06	123	6.0	10.4	145.0	3.72	108.1
F02059	5.9	4.1	2.28	127	77	28	54	20	0	242	13.1	0.37	0.07	282	7.2	9.8	146.7	4.28	108.0
F02060	6.2	4.4	2.44	131	60	30	49	21	0	230	11.4	0.37	0.10	321	6.9	10.3	146.1	3.78	106.4
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	6.0	4.1	2.13	129	62	35	52	21	1	330	13.1	0.38	0.06	257	5.7	9.5	145.7	4.12	108.8
S.D.	0.3	0.3	0.2	9	10	17	8	3	1	235	1.3	0.03	0.02	99	1.0	0.6	1.0	0.36	1.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	KW	AN	KW	DT	DT	AN	KW	KW	AN	DU	AN	DU	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.

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

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

DT: Analysis by Dunnett type mean rank test.

Remeasurement was performed because the first measurement value deviated from the control criteria for laboratory error. The first measurement value was adopted.

Appendix 7 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Blood biochemical analysis of females

Medium dose (BEA 100 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	CPK 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	6.0	4.1	2.16	141	54	61	55	24	0	120	17.4	0.43	0.06	242	5.1	9.4	144.7	4.09	107.4
F03062	5.2	3.5	2.06	121	56	52	46	22	1	220	12.7	0.38	0.03	225	4.4	8.7	145.0	4.22	110.7
F03063	5.6	3.8	2.11	106	65	18	52	32	1	90	14.6	0.37	0.04	301	6.9	9.5	145.5	4.39	108.3
F03064	5.9	4.1	2.28	133	76	21	54	24	1	52	13.4	0.42	0.04	188	6.4	9.5	146.0	4.12	107.6
F03065	5.3	3.5	1.94	105	43	14	63	24	1	189	14.7	0.38	0.03	348	6.3	9.0	146.0	4.35	111.8
F03066	6.2	4.2	2.10	134	88	39	52	23	0	301	10.6	0.33	0.03	206	5.8	9.8	146.0	3.99	108.8
F03067	6.2	4.2	2.10	131	57	23	58	22	0	352	13.2	0.41	0.04	261	6.8	9.7	147.1	4.13	110.3
F03068	5.8	4.0	2.22	139	40	14	52	20	0	283	16.0	0.35	0.03	182	7.3	9.9	147.2	3.90	108.8
F03069	6.2	4.2	2.10	175	59	30	52	20	0	177	12.2	0.45	0.02	343	5.6	10.2	144.2	4.36	106.6
F03070	6.1	4.1	2.05	129	57	17	59	25	0	169	13.8	0.37	0.05	344	7.1	10.4	145.0	4.59	105.0
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.9	4.0	2.11	131	60	29	54	24	0	195	13.9	0.39	0.04	264	6.2	9.6	145.7	4.21	108.5
S.D.	0.4	0.3	0.09	20	14	17	5	3	1	96	1.9	0.04	0.01	66	0.9	0.5	1.0	0.21	2.0
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	KW	AN	KW	DT	DT	AN	KW	KW	AN	DU	AN	DU	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.

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

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

DT: Analysis by Dunnett type mean rank test.

Appendix 7 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Blood biochemical analysis of females

High dose (BEA 500 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	CPK 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
F04071	5.3	3.7	2.31	122	68	34	51	22	1	190	14.3	0.37	0.05	384	6.6	8.5	145.1	4.25	111.3
F04072	5.0	3.5	2.33	124	49	30	88	52 #	1	87	12.5	0.34	0.04	301	5.4	8.5	144.1	3.67	109.7
F04073	5.4	3.9	2.60	120	52	22	68	26	1	78	12.5	0.34	0.07	246	6.5	8.6	145.0	3.94	109.0
F04074	4.7	3.2	2.13	104	43	16	73	30	1	219	21.4	0.43	0.03	354	7.3	8.3	146.5	3.64	109.5
F04075	4.8	3.2	2.00	120	30	11	72	32	0	124	16.5	0.35	0.03	240	7.2	8.3	145.1	4.46	109.7
F04076	5.7	4.0	2.35	135	56	23	68	36	1	150	14.7	0.32	0.04	358	7.4	9.8	147.3	3.79	111.0
F04077	5.6	3.7	1.95	123	43	15	78	32	1	231	20.5	0.43	0.04	389	8.7	9.3	146.5	4.06	109.3
F04078	5.8	3.8	1.90	131	61	23	53	27	0	224	18.2	0.33	0.02	225	6.9	9.6	144.9	4.10	108.5
F04079	5.6	3.8	2.11	113	64	18	67	29	1	117	12.8	0.32	0.04	262	7.1	9.5	145.7	3.93	111.9
F04080	5.3	3.8	2.53	117	48	12	69	30	0	188	16.5	0.46	0.04	244	6.6	9.3	145.3	3.97	108.5
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	5.3	3.7	2.22	121	51	20	69	32	1	161	16.0	0.37	0.04	300	7.0	9.0	145.6	3.98	109.8
S.D.	0.4	0.3	0.24	9	11	8	11	8	0	57	3.2	0.05	0.01	65	0.8	0.6	1.0	0.25	1.2
Significance	**	*	NS	NS	NS	NS	**	**	NS	NS	NS	NS	**	NS	**	NS	NS	NS	NS
Statistical method	DU	DU	KW	KW	AN	KW	DT	DT	AN	KW	KW	AN	DU	AN	DU	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.

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

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

DT: Analysis by Dunnett type mean rank test.

Remeasurement was performed because the first measurement value deviated from the control criteria for laboratory error. The first measurement value was adopted.

Appendix 8

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

Control (vehicle: corn oil)

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)
M01001	586.8	1964.2	3.347	291.3	0.496	1632.4	2.782	1369.7	2.334	16248.2	27.690	1758.1	2.996	1680.5	2.864	3438.6	5.860
M01002	679.1	2174.2	3.202	224.3	0.330	1689.7	2.488	1450.4	2.136	18496.0	27.236	1712.6	2.522	1754.2	2.583	3466.8	5.105
M01003	572.9	1981.6	3.459	344.0	0.600	1499.1	2.617	1390.1	2.426	14129.1	24.662	1400.9	2.445	1516.3	2.647	2917.2	5.092
M01004	557.1	1884.9	3.383	344.6	0.619	1659.7	2.979	1523.7	2.735	16079.8	28.863	1634.8	2.934	1701.0	3.053	3335.8	5.988
M01005	493.0	1995.4	4.047	222.3	0.451	1317.6	2.673	1308.5	2.654	11830.5	23.997	1433.8	2.908	1500.7	3.044	2934.5	5.952
M01006	551.5	2145.6	3.890	212.6	0.385	1485.2	2.693	1492.8	2.707	14917.6	27.049	1847.0	3.349	1865.8	3.383	3712.8	6.732
M01007	582.2	2119.7	3.641	268.8	0.462	1657.2	2.846	1639.0	2.815	15214.0	26.132	1665.2	2.860	1641.1	2.819	3306.3	5.679
M01008	633.0	2031.0	3.209	367.2	0.580	1625.7	2.568	1547.6	2.445	20472.2	32.342	1779.1	2.811	1771.1	2.798	3550.2	5.609
M01009	678.0	2100.1	3.097	302.8	0.447	1823.3	2.689	1450.0	2.139	19957.5	29.436	1759.0	2.594	1714.5	2.529	3473.5	5.123
M01010	632.4	2056.0	3.251	258.3	0.408	1779.2	2.813	1507.9	2.384	16685.8	26.385	1783.9	2.821	1894.8	2.996	3678.7	5.817
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	596.6	2045.3	3.453	283.6	0.478	1616.9	2.715	1468.0	2.478	16403.1	27.379	1677.4	2.824	1704.0	2.872	3381.4	5.696
S.D.	58.9	90.9	0.314	55.7	0.096	148.6	0.144	95.9	0.242	2655.8	2.419	150.0	0.261	129.4	0.258	272.6	0.507

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	854.5	1.456	1641.8	2.798	1660.8	2.830	3302.6	5.628	739.6	1.260	732.8	1.249	1995.3	3.400
M01002	960.0	1.414	1805.1	2.658	1834.5	2.701	3639.6	5.359	311.0	0.458	803.7	1.183	1914.4	2.819
M01003	642.0	1.121	1698.7	2.965	1728.2	3.017	3426.9	5.982	378.6	0.661	702.0	1.225	1719.0	3.001
M01004	722.4	1.297	1776.8	3.189	1792.7	3.218	3569.5	6.407	374.7	0.673	871.0	1.563	1883.6	3.381
M01005	783.7	1.590	1740.1	3.530	1750.7	3.551	3490.8	7.081	656.8	1.332	674.4	1.368	1610.0	3.266
M01006	905.9	1.643	2015.5	3.655	1869.5	3.390	3885.0	7.044	647.9	1.175	633.2	1.148	1944.8	3.526
M01007	843.0	1.448	1717.5	2.950	1743.3	2.994	3460.8	5.944	389.2	0.668	695.4	1.194	1708.4	2.934
M01008	824.5	1.303	2035.9	3.216	2003.5	3.165	4039.4	6.381	365.5	0.577	780.3	1.233	1577.0	2.491
M01009	928.3	1.369	1801.0	2.656	1736.8	2.562	3537.8	5.218	508.4	0.750	1123.9	1.658	2033.4	2.999
M01010	811.2	1.283	1792.2	2.834	1683.4	2.662	3475.6	5.496	630.5	0.997	856.7	1.355	1716.6	2.714
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	827.6	1.392	1802.5	3.045	1780.3	3.009	3582.8	6.054	500.2	0.855	787.3	1.318	1810.3	3.053
S.D.	95.7	0.154	128.4	0.346	100.8	0.326	221.8	0.663	155.5	0.310	141.7	0.171	163.4	0.334

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	586.8	15.5	0.026	31.3	0.053	29.1	0.050	27.7	0.047	56.8	0.097
M01002	679.1	12.8	0.019	33.4	0.049	27.5	0.040	31.1	0.046	58.6	0.086
M01003	572.9	10.4	0.018	27.3	0.048	no data	no data	(19.3)	(0.034)	no data	no data
M01004	557.1	13.7	0.025	34.1	0.061	33.6	0.060	37.7	0.068	71.3	0.128
M01005	493.0	13.1	0.027	17.0	0.034	25.5	0.052	28.0	0.057	53.5	0.109
M01006	551.5	17.4	0.032	23.1	0.042	25.4	0.046	27.9	0.051	53.3	0.097
M01007	582.2	10.5	0.018	26.3	0.045	21.6	0.037	25.7	0.044	47.3	0.081
M01008	633.0	13.8	0.022	25.7	0.041	27.1	0.043	25.8	0.041	52.9	0.084
M01009	678.0	12.2	0.018	20.8	0.031	29.2	0.043	26.5	0.039	55.7	0.082
M01010	632.4	13.9	0.022	25.9	0.041	34.6	0.055	38.5	0.061	73.1	0.116
Number of males	10	10	10	10	10	9	9	9	9	9	9
Mean	596.6	13.3	0.023	26.5	0.045	28.2	0.470	29.9	0.050	58.1	0.098
S.D.	58.9	2.1	0.005	5.4	0.009	4.1	0.007	4.9	0.010	8.6	0.017

- : The data was excluded because the right side of adrenal gland did not obtained.

The figure in parentheses is reference data.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

Low dose (BEA 20 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)
M02011	534.8	1984.0	3.710	245.9	0.460	1502.2	2.809	1292.0	2.416	13146.0	24.581	1529.4	2.860	1519.1	2.841	3048.5	5.700
M02012	522.1	2130.3	4.080	348.7	0.668	1542.0	2.953	1359.6	2.604	14450.3	27.677	1495.2	2.864	1578.6	3.024	3073.8	5.887
M02013	619.4	2090.4	3.375	207.7	0.335	1591.0	2.569	1543.2	2.491	15754.3	25.435	1986.5	3.207	2036.9	3.289	4023.4	6.496
M02014	610.9	2017.5	3.303	178.5	0.292	1792.1	2.934	1470.4	2.407	20084.1	32.876	1871.5	3.064	1888.7	3.092	3760.2	6.155
M02015	575.9	2107.1	3.659	333.9	0.580	1508.0	2.619	1462.3	2.539	14014.6	24.335	1566.9	2.721	1536.1	2.667	3103.0	5.388
M02016	560.8	2038.6	3.635	250.9	0.447	1440.4	2.568	1497.3	2.670	16311.9	29.087	1722.9	3.072	1651.0	2.944	3373.9	6.016
M02017	664.8	2004.2	3.015	292.8	0.440	1644.7	2.474	1565.9	2.355	18364.2	27.624	1683.6	2.532	1560.6	2.347	3244.2	4.880
M02018	488.1	2061.2	4.223	196.7	0.403	1550.9	3.177	1304.4	2.672	13253.4	27.153	1670.4	3.422	1547.7	3.171	3218.1	6.593
M02019	545.8	1928.8	3.534	394.5	0.723	1495.2	2.739	1439.8	2.638	15009.0	27.499	1609.8	2.949	1553.0	2.845	3162.8	5.795
M02020	654.7	1924.8	2.940	422.2	0.645	1629.4	2.489	1378.4	2.105	19002.8	29.025	1439.8	2.199	1541.0	2.354	2980.8	4.553
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	577.7	2028.7	3.547	287.2	0.499	1569.6	2.733	1431.3	2.490	15939.1	27.529	1657.6	2.889	1641.3	2.857	3298.9	5.746
S.D.	58.3	70.7	0.412	85.0	0.147	100.5	0.232	94.9	0.177	2459.0	2.510	169.9	0.347	176.7	0.321	337.4	0.654
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	DU	AN	AN	AN	DU	AN	DU	AN	DU	AN	DU

Low dose (BEA 20 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	768.7	1.437	1717.1	3.211	1737.1	3.248	3454.2	6.459	483.3	0.904	689.3	1.289	1413.0	2.642
M02012	697.3	1.336	1561.0	2.990	1562.6	2.993	3123.6	5.983	598.0	1.145	677.8	1.298	1219.0	2.335
M02013	790.7	1.277	1640.5	2.649	1629.4	2.631	3269.9	5.279	763.2	1.232	812.0	1.311	2166.9	3.498
M02014	823.8	1.349	1692.3	2.770	1600.1	2.619	3292.4	5.389	512.8	0.839	564.3	0.924	1812.5	2.967
M02015	859.6	1.493	2016.0	3.501	1976.5	3.432	3992.5	6.933	444.4	0.772	735.1	1.276	1664.1	2.890
M02016	880.5	1.570	1690.6	3.015	1613.4	2.877	3304.0	5.892	726.5	1.295	656.6	1.171	1493.5	2.663
M02017	989.1	1.488	2105.2	3.167	2035.1	3.061	4140.3	6.228	695.4	1.046	777.2	1.169	1809.0	2.721
M02018	633.1	1.297	1784.6	3.656	1759.4	3.605	3544.0	7.261	625.1	1.281	675.8	1.385	1633.2	3.346
M02019	802.9	1.471	1714.8	3.142	1680.6	3.079	3395.4	6.221	456.5	0.836	773.6	1.417	1729.1	3.168
M02020	815.5	1.246	1785.5	2.727	1741.8	2.660	3527.3	5.388	597.3	0.912	809.3	1.236	1484.9	2.268
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	806.1	1.396	1770.8	3.083	1733.6	3.021	3504.4	6.103	590.3	1.026	717.1	1.248	1642.5	2.850
S.D.	97.6	0.109	167.3	0.326	158.4	0.339	323.9	0.662	114.2	0.199	78.6	0.139	262.2	0.406
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

Low dose (BEA 20 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	534.8	11.5	0.022	21.9	0.041	24.1	0.045	29.3	0.055	53.4	0.100
M02012	522.1	10.7	0.020	26.4	0.051	23.2	0.044	27.9	0.053	51.1	0.098
M02013	619.4	14.9	0.024	25.8	0.042	30.8	0.050	28.8	0.046	59.6	0.096
M02014	610.9	10.6	0.017	23.0	0.038	37.5	0.061	41.0	0.067	78.5	0.128
M02015	575.9	11.1	0.019	30.7	0.053	26.3	0.046	29.2	0.051	55.5	0.096
M02016	560.8	15.4	0.027	25.4	0.045	35.9	0.064	37.1	0.066	73.0	0.130
M02017	664.8	12.1	0.018	25.4	0.038	35.0	0.053	35.8	0.054	70.8	0.106
M02018	488.1	10.2	0.021	24.2	0.050	25.5	0.052	24.4	0.050	49.9	0.102
M02019	545.8	14.4	0.026	25.7	0.047	23.0	0.042	19.9	0.036	42.9	0.079
M02020	654.7	12.7	0.019	24.4	0.037	22.6	0.035	26.7	0.041	49.3	0.075
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	577.7	12.4	0.021	25.3	0.044	28.4	0.049	30.0	0.052	58.4	0.101
S.D.	58.3	1.9	0.003	2.3	0.006	5.9	0.009	6.3	0.010	11.8	0.018
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	KW	AN	KW	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).

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

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

Medium dose (BEA 100 mg/kg)

Male 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)
M03021	557.2	1910.7	3.429	399.6	0.717	1530.9	2.747	1450.8	2.604	14910.9	26.760	1707.0	3.064	1697.5	3.046	3404.5	6.110
M03022	585.8	2021.2	3.450	264.7	0.452	1497.2	2.556	1528.0	2.608	13564.2	23.155	1865.5	3.185	2020.9	3.450	3886.4	6.634
M03023	642.6	2111.4	3.286	287.5	0.447	1964.6	3.057	1428.2	2.223	17110.0	26.626	1803.8	2.807	1786.8	2.781	3590.6	5.588
M03024	496.5	2130.3	4.291	360.0	0.725	1340.5	2.700	1261.1	2.540	12069.5	24.309	1261.0	2.540	1328.6	2.676	2589.6	5.216
M03025	531.2	2078.3	3.912	238.6	0.449	1596.8	3.006	1366.8	2.573	13471.7	25.361	1571.0	2.957	1581.5	2.977	3152.5	5.935
M03026	659.6	2000.1	3.032	294.6	0.447	1690.7	2.563	1503.1	2.279	18244.4	27.660	1890.7	2.866	1876.7	2.845	3767.4	5.712
M03027	484.4	1935.9	3.996	268.0	0.553	1522.9	3.144	1288.0	2.659	13372.4	27.606	1902.5	3.928	1790.6	3.697	3693.1	7.624
M03028	488.9	1949.9	3.988	252.5	0.516	1366.1	2.794	1388.9	2.841	14186.9	29.018	1378.0	2.819	1389.8	2.843	2767.8	5.661
M03029	619.5	2092.3	3.377	463.0	0.747	1646.8	2.658	1511.1	2.439	16254.5	26.238	1794.2	2.896	1813.6	2.928	3607.8	5.824
M03030	562.7	2090.7	3.715	210.1	0.373	1592.4	2.830	1596.5	2.837	13923.9	24.745	1510.8	2.685	1528.3	2.716	3039.1	5.401
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	562.8	2032.1	3.648	303.9	0.543	1574.9	2.806	1432.3	2.560	14710.8	26.148	1668.5	2.975	1681.4	2.996	3349.9	5.971
S.D.	63.7	79.6	0.394	79.2	0.138	176.5	0.204	107.5	0.205	1920.0	1.770	226.9	0.381	220.4	0.330	442.2	0.701
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	DU	AN	AN	AN	DU	AN	DU	AN	DU	AN	DU

Medium dose (BEA 100 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)
M03021	782.9	1.405	1611.6	2.892	1660.3	2.980	3271.9	5.872	543.8	0.976	649.1	1.165	1632.4	2.930
M03022	726.3	1.240	1665.2	2.843	1627.3	2.778	3292.5	5.621	833.7	1.423	942.5	1.609	2132.1	3.640
M03023	1061.3	1.652	1698.0	2.642	1717.2	2.672	3415.2	5.315	550.1	0.856	791.3	1.231	1270.6	1.977
M03024	826.1	1.664	1654.9	3.333	1673.3	3.370	3328.2	6.703	953.8	1.921	791.9	1.595	1745.8	3.516
M03025	765.8	1.442	1508.8	2.840	1441.7	2.714	2950.5	5.554	505.1	0.951	641.0	1.207	1510.9	2.844
M03026	871.7	1.322	1793.2	2.719	1810.8	2.745	3604.0	5.464	800.2	1.213	764.8	1.159	2176.0	3.299
M03027	897.9	1.854	1672.9	3.454	1749.2	3.611	3422.1	7.065	643.9	1.329	743.1	1.534	1532.0	3.163
M03028	709.1	1.450	1760.7	3.601	1797.0	3.676	3557.7	7.277	420.7	0.861	636.5	1.302	1577.0	3.226
M03029	938.3	1.515	1858.2	3.000	1886.5	3.045	3744.7	6.045	411.6	0.664	807.9	1.304	1808.5	2.919
M03030	756.2	1.344	1848.7	3.285	1827.7	3.248	3676.4	6.533	615.7	1.094	712.3	1.266	1551.3	2.757
Number of males	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	833.6	1.489	1707.2	3.061	1719.1	3.084	3426.3	6.145	627.9	1.129	748.0	1.337	1693.7	3.027
S.D.	109.9	0.186	109.2	0.332	127.4	0.375	233.5	0.703	181.5	0.362	94.6	0.175	282.2	0.469
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN

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.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

Medium dose (BEA 100 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	557.2	15.0	0.027	25.4	0.046	21.6	0.039	22.1	0.040	43.7	0.078
M03022	585.8	18.4	0.031	30.2	0.052	21.9	0.037	26.1	0.045	48.0	0.082
M03023	642.6	11.0	0.017	21.0	0.033	26.4	0.041	27.7	0.043	54.1	0.084
M03024	496.5	10.3	0.021	24.5	0.049	21.3	0.043	21.6	0.044	42.9	0.086
M03025	531.2	10.8	0.020	26.0	0.049	23.1	0.043	22.1	0.042	45.2	0.085
M03026	659.6	12.5	0.019	40.3	0.061	24.2	0.037	24.2	0.037	48.4	0.073
M03027	484.4	13.8	0.028	26.3	0.054	26.8	0.055	27.8	0.057	54.6	0.113
M03028	488.9	13.9	0.028	18.0	0.037	23.2	0.047	25.4	0.052	48.6	0.099
M03029	619.5	11.9	0.019	33.1	0.053	25.9	0.042	28.8	0.046	54.7	0.088
M03030	562.7	12.5	0.022	20.6	0.037	32.2	0.057	30.3	0.054	62.5	0.111
Number of males	10	10	10	10	10	10	10	10	10	10	10
Mean	562.8	13.0	0.023	26.5	0.047	24.7	0.044	25.6	0.046	50.3	0.090
S.D.	63.7	2.4	0.005	6.6	0.009	3.3	0.007	3.1	0.006	6.1	0.013
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	KW	AN	KW	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).

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

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

High dose (BEA 500 mg/kg)

Male 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)
M04031	486.6	1996.7	4.103	162.5	0.334	1525.4	3.135	1228.2	2.524	15109.0	31.050	1712.2	3.519	1722.1	3.539	3434.3	7.058
M04032	520.1	2075.9	3.991	273.2	0.525	1575.7	3.030	1434.8	2.759	17435.7	33.524	2180.0	4.192	2165.5	4.164	4345.5	8.355
M04033	497.7	1977.0	3.972	226.4	0.455	1471.1	2.956	1355.7	2.724	13777.9	27.683	1476.0	2.966	1527.9	3.070	3003.9	6.036
M04034	561.6	1976.1	3.519	355.7	0.633	1668.1	2.970	1527.1	2.719	17272.9	30.757	1822.2	3.245	1936.6	3.448	3758.8	6.693
M04035	532.8	2113.7	3.967	315.4	0.592	1522.1	2.857	1354.9	2.543	16052.4	30.128	1840.0	3.453	1790.6	3.361	3630.6	6.814
M04037	526.5	2007.8	3.813	335.8	0.638	1645.2	3.125	1374.5	2.611	17415.8	33.078	1812.9	3.443	1986.8	3.774	3799.7	7.217
M04038	537.3	2069.7	3.852	241.6	0.450	1507.8	2.806	1551.8	2.888	18147.1	33.775	1967.3	3.661	2040.5	3.798	4007.8	7.459
M04039	509.1	1961.7	3.853	207.0	0.407	1351.8	2.655	1304.6	2.563	16600.3	32.607	1703.7	3.346	1664.5	3.269	3368.2	6.616
M04040	459.7	2057.8	4.476	352.3	0.766	1455.4	3.166	1429.5	3.110	14150.4	30.782	1637.8	3.563	1668.5	3.630	3306.3	7.192
Number of males	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	514.6	2026.3	3.950	274.4	0.533	1524.7	2.967	1395.7	2.716	16217.9	31.487	1794.7	3.488	1833.7	3.561	3628.3	7.049
S.D.	30.3	54.0	0.256	69.4	0.136	97.2	0.170	102.7	0.190	1556.6	1.959	200.8	0.333	209.4	0.326	403.7	0.644
Significance	**	NS	*	NS	NS	NS	*	NS	NS	NS	**	NS	**	NS	**	NS	**
Statistical method	DU	AN	DU	AN	AN	AN	DU	AN	AN	AN	DU	AN	DU	AN	DU	AN	DU

High dose (BEA 500 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)
M04031	1178.3	2.421	1735.5	3.567	1752.4	3.601	3487.9	7.168	538.5	1.107	563.3	1.158	1719.8	3.534
M04032	1148.8	2.209	1632.4	3.139	1679.7	3.230	3312.1	6.368	541.3	1.041	779.5	1.499	1947.8	3.745
M04033	1242.2	2.496	1752.1	3.520	1736.6	3.489	3488.7	7.010	737.3	1.481	544.5	1.094	1714.4	3.445
M04034	1745.7	3.108	1673.1	2.979	1661.4	2.958	3334.5	5.938	555.9	0.990	639.6	1.139	1954.9	3.481
M04035	1466.1	2.752	1799.2	3.377	1861.9	3.495	3661.1	6.871	781.5	1.467	700.1	1.314	1941.6	3.644
M04037	1328.7	2.524	1900.4	3.609	1870.5	3.553	3770.9	7.162	287.0	0.545	577.8	1.097	1591.5	3.023
M04038	1330.0	2.475	1791.3	3.334	1773.9	3.302	3565.2	6.635	607.6	1.131	633.1	1.178	1596.5	2.971
M04039	1077.4	2.116	1600.8	3.144	1548.1	3.041	3148.9	6.185	573.3	1.126	660.3	1.297	1544.5	3.034
M04040	932.1	2.028	1426.9	3.104	1456.7	3.169	2883.6	6.273	599.1	1.303	627.3	1.365	1343.9	2.923
Number of males	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	1272.1	2.459	1701.3	3.308	1704.6	3.315	3405.9	6.623	580.2	1.132	636.2	1.238	1706.1	3.311
S.D.	236.4	0.332	137.8	0.227	136.4	0.232	271.6	0.454	139.7	0.282	72.8	0.139	211.7	0.320
Significance	**	**	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS
Statistical method	DT	DT	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

DT: Analysis by Dunnett type mean rank test.

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of males

High dose (BEA 500 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	486.6	12.9	0.027	29.0	0.060	27.6	0.057	29.8	0.061	57.4	0.118
M04032	520.1	12.6	0.024	25.6	0.049	25.3	0.049	24.4	0.047	49.7	0.096
M04033	497.7	9.6	0.019	31.1	0.062	29.2	0.059	33.2	0.067	62.4	0.125
M04034	561.6	10.4	0.019	21.1	0.038	20.9	0.037	22.3	0.040	43.2	0.077
M04035	532.8	9.3	0.017	21.3	0.040	25.1	0.047	25.6	0.048	50.7	0.095
M04037	526.5	10.0	0.019	32.7	0.062	19.4	0.037	22.9	0.043	42.3	0.080
M04038	537.3	12.9	0.024	23.7	0.044	29.8	0.055	28.9	0.054	58.7	0.109
M04039	509.1	10.8	0.021	31.7	0.062	22.1	0.043	22.2	0.044	44.3	0.087
M04040	459.7	13.8	0.030	37.5	0.082	20.4	0.044	22.7	0.049	43.1	0.094
Number of males	9	9	9	9	9	9	9	9	9	9	9
Mean	514.6	11.4	0.022	28.2	0.055	24.4	0.048	25.8	0.050	50.2	0.098
S.D.	30.3	1.7	0.004	5.6	0.014	3.9	0.008	4.0	0.009	7.7	0.016
Significance	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	KW	AN	KW	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 2-butoxyethyl acetate in rats

Organ weight of females

Control (vehicle: corn oil)

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)
F01041	316.3	1938.1	6.127	264.1	0.835	863.0	2.728	1134.0	3.585	6998.9	22.127	898.8	2.842	876.0	2.770	1774.8	5.611
F01042	226.8	1870.4	8.247	347.3	1.531	771.7	3.403	833.5	3.675	6188.8	27.287	781.5	3.446	751.7	3.314	1533.2	6.760
F01043	282.7	1876.4	6.637	175.5	0.621	904.2	3.198	1039.0	3.675	7327.3	25.919	868.6	3.073	790.1	2.795	1658.7	5.867
F01044	273.3	1841.9	6.739	264.0	0.966	806.1	2.950	1053.9	3.856	6824.0	24.969	804.5	2.944	841.1	3.078	1645.6	6.021
F01045	255.9	1823.8	7.127	218.6	0.854	821.7	3.211	1073.1	4.193	5974.4	23.347	746.7	2.918	757.0	2.958	1503.7	5.876
F01046	291.1	1860.3	6.391	299.9	1.030	922.8	3.170	979.8	3.366	7307.3	25.102	935.9	3.215	913.5	3.138	1849.4	6.353
F01047	300.9	1728.8	5.745	199.1	0.662	986.0	3.277	1056.6	3.511	7328.0	24.354	940.7	3.126	919.2	3.055	1859.9	6.181
F01048	279.3	1843.8	6.602	150.9	0.540	823.1	2.947	999.0	3.577	6057.7	21.689	879.5	3.149	896.5	3.210	1776.0	6.359
F01049	283.8	1965.3	6.925	176.0	0.620	892.4	3.144	981.0	3.457	7418.7	26.141	960.1	3.383	930.3	3.278	1890.4	6.661
F01050	236.9	1793.6	7.571	246.7	1.041	818.7	3.456	1019.4	4.303	5967.9	25.192	833.5	3.518	814.0	3.436	1647.5	6.954
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	274.7	1854.2	6.811	234.2	0.870	861.0	3.148	1016.9	3.720	6739.3	24.613	865.0	3.161	848.9	3.103	1713.9	6.264
S.D.	27.8	67.3	0.716	61.7	0.294	65.0	0.221	79.5	0.310	623.5	1.773	72.1	0.230	67.8	0.218	136.4	0.434

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	695.9	2.200	48.6	0.154	47.2	0.149	95.8	0.303	381.5	1.206	430.7	1.362
F01042	565.6	2.494	37.5	0.165	35.8	0.158	73.3	0.323	989.2	4.362	414.1	1.826
F01043	450.6	1.594	28.2	0.100	42.1	0.149	70.3	0.249	502.4	1.777	458.2	1.621
F01044	463.5	1.696	29.3	0.107	27.2	0.100	56.5	0.207	423.1	1.548	409.4	1.498
F01045	447.1	1.747	38.9	0.152	34.1	0.133	73.0	0.285	565.4	2.209	488.8	1.910
F01046	562.1	1.931	45.0	0.155	39.4	0.135	84.4	0.290	483.9	1.662	498.2	1.711
F01047	587.2	1.951	43.0	0.143	32.0	0.106	75.0	0.249	472.1	1.569	412.1	1.370
F01048	510.1	1.826	24.3	0.087	29.0	0.104	53.3	0.191	907.4	3.249	377.6	1.352
F01049	562.1	1.981	56.4	0.199	29.3	0.103	85.7	0.302	807.3	2.845	440.1	1.551
F01050	423.4	1.787	30.2	0.127	43.1	0.182	73.3	0.309	498.6	2.105	408.5	1.724
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	526.8	1.921	38.1	0.139	35.9	0.132	74.1	0.271	603.1	2.253	433.8	1.593
S.D.	83.9	0.264	10.3	0.034	6.8	0.028	12.8	0.045	215.7	0.969	38.1	0.200

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate 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	316.3	15.7	0.050	26.3	0.083	29.1	0.092	26.8	0.085	55.9	0.177
F01042	226.8	16.4	0.072	18.3	0.081	28.7	0.127	28.0	0.123	56.7	0.250
F01043	282.7	14.8	0.052	20.8	0.074	27.8	0.098	23.0	0.081	50.8	0.180
F01044	273.3	21.5	0.079	23.2	0.085	22.2	0.081	26.1	0.095	48.3	0.177
F01045	255.9	12.5	0.049	22.3	0.087	26.9	0.105	29.4	0.115	56.3	0.220
F01046	291.1	14.2	0.049	37.5	0.129	21.1	0.072	25.7	0.088	46.8	0.161
F01047	300.9	17.8	0.059	26.1	0.087	30.1	0.100	32.3	0.107	62.4	0.207
F01048	279.3	21.7	0.078	16.5	0.059	20.6	0.074	24.7	0.088	45.3	0.162
F01049	283.8	14.9	0.053	22.7	0.080	32.9	0.116	30.7	0.108	63.6	0.224
F01050	236.9	13.2	0.056	22.0	0.093	27.5	0.116	28.1	0.119	55.6	0.235
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	274.7	16.3	0.060	23.6	0.086	26.7	0.098	27.5	0.101	54.2	0.199
S.D.	27.8	3.2	0.012	5.8	0.018	4.1	0.019	2.8	0.015	6.2	0.032

Appendix 8 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Organ weight of females

Low dose (BEA 20 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)
F02051	294.0	1665.6	5.665	275.5	0.937	888.2	3.021	946.5	3.219	7106.8	24.173	839.0	2.854	827.8	2.816	1666.8	5.669
F02052	273.2	1812.2	6.633	178.1	0.652	854.9	3.129	1012.8	3.707	6977.1	25.538	927.5	3.395	920.2	3.368	1847.7	6.763
F02053	255.9	1833.9	7.166	193.8	0.757	792.9	3.098	1072.2	4.190	6365.6	24.875	787.9	3.079	764.2	2.986	1552.1	6.065
F02054	316.2	1868.7	5.910	293.9	0.929	981.4	3.104	1113.3	3.521	8734.7	27.624	1018.3	3.220	946.7	2.994	1965.0	6.214
F02055	342.4	1859.2	5.430	270.7	0.791	964.8	2.818	1079.8	3.154	8822.9	25.768	1096.2	3.202	1015.8	2.967	2112.0	6.168
F02056	278.8	1795.4	6.440	211.4	0.758	1001.3	3.591	1091.2	3.914	7503.9	26.915	896.0	3.214	837.3	3.003	1733.3	6.217
F02057	235.4	1833.4	7.788	213.8	0.908	762.1	3.237	960.6	4.081	6136.8	26.070	834.3	3.544	809.4	3.438	1643.7	6.983
F02058	288.1	1784.5	6.194	157.9	0.548	1004.0	3.485	1047.4	3.636	7889.5	27.385	867.9	3.012	875.9	3.040	1743.8	6.053
F02059	257.5	1944.5	7.551	157.7	0.612	768.9	2.986	1051.2	4.082	6010.0	23.340	831.9	3.231	858.9	3.336	1690.8	6.566
F02060	328.2	1821.3	5.549	283.6	0.864	912.4	2.780	1075.8	3.278	8372.5	25.510	967.1	2.947	973.5	2.966	1940.6	5.913
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	287.0	1821.9	6.433	223.6	0.776	893.1	3.125	1045.1	3.678	7392.0	25.720	906.6	3.170	883.0	3.091	1789.6	6.261
S.D.	34.0	71.1	0.841	53.0	0.137	95.1	0.259	55.4	0.382	1046.9	1.366	96.4	0.206	79.3	0.209	172.8	0.399
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	AN	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DU

Low dose (BEA 20 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	415.4	1.413	60.3	0.205	58.1	0.198	118.4	0.403	608.5	2.070	410.2	1.395
F02052	397.5	1.455	35.0	0.128	30.3	0.111	65.3	0.239	607.1	2.222	398.6	1.459
F02053	467.5	1.827	41.5	0.162	39.4	0.154	80.9	0.316	440.3	1.721	486.3	1.900
F02054	576.8	1.824	35.4	0.112	42.8	0.135	78.2	0.247	843.4	2.667	503.2	1.591
F02055	611.7	1.787	42.5	0.124	37.0	0.108	79.5	0.232	483.6	1.412	457.2	1.335
F02056	521.3	1.870	35.8	0.128	40.9	0.147	76.7	0.275	448.6	1.609	443.6	1.591
F02057	474.8	2.017	24.5	0.104	26.8	0.114	51.3	0.218	452.9	1.924	442.1	1.878
F02058	525.3	1.823	53.2	0.185	48.2	0.167	101.4	0.352	486.0	1.687	417.9	1.451
F02059	375.6	1.459	35.7	0.139	29.2	0.113	64.9	0.252	342.7	1.331	427.3	1.659
F02060	582.9	1.776	40.0	0.122	37.0	0.113	77.0	0.235	638.9	1.947	470.5	1.434
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	494.9	1.725	40.4	0.141	39.0	0.136	79.4	0.277	535.2	1.859	445.7	1.569
S.D.	82.3	0.206	10.1	0.033	9.4	0.030	18.9	0.061	142.1	0.399	33.8	0.195
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	KW	KW	KW	AN	KW	AN	AN	KW	AN	AN

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

NS: Not significantly different from the control group.

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

KW: Analysis by Kruskal-Wallis' test (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 2-butoxyethyl acetate in rats

Organ weight of females

Low dose (BEA 20 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	294.0	18.2	0.062	18.5	0.063	29.2	0.099	32.4	0.110	61.6	0.210
F02052	273.2	13.8	0.051	18.5	0.068	27.1	0.099	26.5	0.097	53.6	0.196
F02053	255.9	18.7	0.073	17.6	0.069	24.6	0.096	25.9	0.101	50.5	0.197
F02054	316.2	19.7	0.062	22.1	0.070	27.4	0.087	28.1	0.089	55.5	0.176
F02055	342.4	20.4	0.060	21.0	0.061	34.2	0.100	37.6	0.110	71.8	0.210
F02056	278.8	16.9	0.061	23.2	0.083	24.8	0.089	25.2	0.090	50.0	0.179
F02057	235.4	14.2	0.060	21.0	0.089	24.9	0.106	27.0	0.115	51.9	0.220
F02058	288.1	19.7	0.068	24.0	0.083	29.0	0.101	26.7	0.093	55.7	0.193
F02059	257.5	11.9	0.046	17.5	0.068	25.4	0.099	24.0	0.093	49.4	0.192
F02060	328.2	14.5	0.044	19.8	0.060	33.0	0.101	35.3	0.108	68.3	0.208
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	287.0	16.8	0.059	20.3	0.071	28.0	0.098	28.9	0.101	56.8	0.198
S.D.	34.0	3.0	0.009	2.3	0.010	3.4	0.006	4.6	0.010	7.9	0.014
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DT	AN	KW	AN	AN	KW	AN	AN	AN	AN

NS: Not significantly different from the control group.

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 2-butoxyethyl acetate in rats

Organ weight of females

Medium dose (BEA 100 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)
F03061	292.8	1964.7	6.710	182.9	0.625	905.5	3.093	1082.4	3.697	8486.1	28.983	990.2	3.382	941.5	3.216	1931.7	6.597
F03062	254.4	1913.5	7.522	317.4	1.248	829.7	3.261	951.3	3.739	6756.6	26.559	814.9	3.203	792.0	3.113	1606.9	6.316
F03063	220.8	1738.2	7.872	148.4	0.672	796.8	3.609	948.8	4.297	6418.6	29.070	764.1	3.461	748.6	3.390	1512.7	6.851
F03064	273.5	1833.3	6.703	182.8	0.668	832.3	3.043	1065.0	3.894	7909.3	28.919	934.9	3.418	900.3	3.292	1835.2	6.710
F03065	271.8	1750.3	6.440	476.9	1.755	846.8	3.116	996.4	3.666	7163.9	26.357	960.5	3.534	964.2	3.547	1924.7	7.081
F03066	308.8	1938.2	6.277	313.6	1.016	983.8	3.186	987.9	3.199	8984.3	29.094	1010.7	3.273	956.8	3.098	1967.5	6.371
F03067	295.5	1861.1	6.298	232.5	0.787	927.6	3.139	1074.2	3.635	7952.6	26.912	972.1	3.290	953.2	3.226	1925.3	6.515
F03068	272.2	1906.0	7.002	317.1	1.165	843.7	3.100	1115.6	4.098	8238.9	30.268	993.8	3.651	917.3	3.370	1911.1	7.021
F03069	330.5	1970.1	5.961	324.7	0.982	962.5	2.912	1093.2	3.308	8438.5	25.533	965.2	2.920	962.5	2.912	1927.7	5.833
F03070	272.3	1886.2	6.927	313.7	1.152	977.8	3.591	1159.7	4.259	8358.9	30.697	1006.5	3.696	1005.1	3.691	2011.6	7.387
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	279.3	1876.2	6.771	281.0	1.007	890.7	3.205	1047.5	3.779	7870.8	28.239	941.3	3.383	914.2	3.286	1855.4	6.668
S.D.	30.1	81.5	0.586	96.8	0.347	69.2	0.227	72.0	0.367	828.2	1.765	84.0	0.228	81.5	0.227	163.4	0.445
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	**	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	KW	AN	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DU

Medium dose (BEA 100 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	783.3	2.675	49.7	0.170	48.7	0.166	98.4	0.336	421.9	1.441	428.9	1.465
F03062	557.1	2.190	37.2	0.146	33.5	0.132	70.7	0.278	1016.3	3.995	390.8	1.536
F03063	592.2	2.682	35.3	0.160	29.6	0.134	64.9	0.294	616.6	2.793	380.2	1.722
F03064	602.6	2.203	32.4	0.118	25.7	0.094	58.1	0.212	418.5	1.530	447.9	1.638
F03065	503.0	1.851	42.1	0.155	53.9	0.198	96.0	0.353	453.5	1.669	443.3	1.631
F03066	614.8	1.991	41.0	0.133	31.4	0.102	72.4	0.234	568.6	1.841	409.4	1.326
F03067	596.8	2.020	35.1	0.119	44.8	0.152	79.9	0.270	585.7	1.982	464.5	1.572
F03068	562.1	2.065	51.6	0.190	40.0	0.147	91.6	0.337	532.4	1.956	424.6	1.560
F03069	561.6	1.699	46.7	0.141	41.5	0.126	88.2	0.267	361.1	1.093	434.3	1.314
F03070	640.7	2.353	48.1	0.177	51.5	0.189	99.6	0.366	443.3	1.628	421.4	1.548
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	601.4	2.173	41.9	0.151	40.1	0.144	82.0	0.295	541.8	1.993	424.5	1.531
S.D.	74.3	0.323	6.8	0.024	9.7	0.034	14.9	0.052	186.6	0.833	25.7	0.131
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	KW	KW	KW	AN	KW	AN	AN	KW	AN	AN

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

NS: Not significantly different from the control group.

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

KW: Analysis by Kruskal-Wallis' test (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 2-butoxyethyl acetate in rats

Organ weight of females

Medium dose (BEA 100 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	292.8	15.9	0.054	19.4	0.066	25.2	0.086	25.4	0.087	50.6	0.173
F03062	254.4	15.2	0.060	16.1	0.063	27.8	0.109	28.7	0.113	56.5	0.222
F03063	220.8	14.8	0.067	20.1	0.091	24.2	0.110	26.5	0.120	50.7	0.230
F03064	273.5	17.2	0.063	16.3	0.060	28.6	0.105	31.4	0.115	60.0	0.219
F03065	271.8	15.1	0.056	18.6	0.068	30.3	0.111	28.8	0.106	59.1	0.217
F03066	308.8	17.1	0.055	24.3	0.079	32.6	0.106	34.3	0.111	66.9	0.217
F03067	295.5	19.9	0.067	19.1	0.065	34.0	0.115	35.5	0.120	69.5	0.235
F03068	272.2	16.6	0.061	18.9	0.069	34.0	0.125	28.6	0.105	62.6	0.230
F03069	330.5	16.7	0.051	19.9	0.060	32.3	0.098	29.5	0.089	61.8	0.187
F03070	272.3	21.6	0.079	24.2	0.089	33.4	0.123	33.2	0.122	66.6	0.245
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	279.3	17.0	0.061	19.7	0.071	30.2	0.109	30.2	0.109	60.4	0.218
S.D.	30.1	2.2	0.008	2.8	0.011	3.6	0.011	3.3	0.012	6.5	0.022
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DT	AN	KW	AN	AN	KW	AN	AN	AN	AN

NS: Not significantly different from the control group.

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 2-butoxyethyl acetate in rats

Organ weight of females

High dose (BEA 500 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	263.2	1874.5	7.122	317.5	1.206	913.2	3.470	940.8	3.574	9477.4	36.008	1041.6	3.957	1018.4	3.869	2060.0	7.827
F04072	296.8	1797.3	6.056	316.3	1.066	1033.4	3.482	1229.8	4.144	9966.0	33.578	1022.9	3.446	1053.3	3.549	2076.2	6.995
F04073	306.9	1842.5	6.004	261.8	0.853	1008.9	3.287	1103.9	3.597	10361.1	33.761	1242.5	4.049	1180.0	3.845	2422.5	7.893
F04074	256.6	1728.1	6.735	240.5	0.937	757.1	2.951	949.8	3.701	8508.8	33.160	942.8	3.674	906.7	3.534	1849.5	7.208
F04075	262.8	1769.3	6.732	183.1	0.697	828.8	3.154	998.3	3.799	8701.6	33.111	947.6	3.606	963.8	3.667	1911.4	7.273
F04076	281.1	2006.1	7.137	277.8	0.988	934.6	3.325	1132.8	4.030	10649.9	37.887	980.7	3.489	995.6	3.542	1976.3	7.031
F04077	276.5	1948.0	7.045	234.1	0.847	939.0	3.396	1075.3	3.889	10258.4	37.101	941.9	3.407	943.5	3.412	1885.4	6.819
F04078	293.3	1737.2	5.923	207.1	0.706	1093.8	3.729	1108.1	3.778	10591.5	36.111	1133.5	3.865	1104.6	3.766	2238.1	7.631
F04079	262.0	1802.0	6.878	257.7	0.984	980.8	3.744	1023.6	3.907	10114.6	38.605	1067.1	4.073	1048.6	4.002	2115.7	8.075
F04080	247.1	1762.6	7.133	142.2	0.575	883.0	3.573	993.5	4.021	8793.6	35.587	924.1	3.740	868.0	3.513	1792.1	7.253
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	274.6	1826.8	6.677	243.8	0.886	937.3	3.411	1055.6	3.844	9742.3	35.491	1024.5	3.731	1008.3	3.670	2032.7	7.401
S.D.	19.6	91.9	0.495	55.6	0.190	99.2	0.247	90.9	0.189	813.6	2.012	101.6	0.247	93.6	0.192	192.8	0.428
Significance	NS	NS	NS	NS	NS	NS	*	NS	NS	**	**	**	**	**	**	**	**
Statistical method	AN	AN	AN	AN	KW	AN	DU	AN	AN	DU	DU	DU	DU	DU	DU	DU	DU

High dose (BEA 500 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)
F04071	762.7	2.898	35.5	0.135	32.0	0.122	67.5	0.256	585.1	2.223	346.0	1.315
F04072	1060.3	3.572	35.4	0.119	29.1	0.098	64.5	0.217	671.1	2.261	426.6	1.437
F04073	1365.6	4.450	40.6	0.132	32.8	0.107	73.4	0.239	559.2	1.822	389.7	1.270
F04074	821.4	3.201	38.0	0.148	38.2	0.149	76.2	0.297	545.7	2.127	443.8	1.730
F04075	989.7	3.766	35.1	0.134	32.4	0.123	67.5	0.257	320.8	1.221	444.2	1.690
F04076	1038.4	3.694	35.6	0.127	30.9	0.110	66.5	0.237	427.7	1.522	445.7	1.586
F04077	1302.6	4.711	41.5	0.150	36.3	0.131	77.8	0.281	822.6	2.975	449.2	1.625
F04078	1099.5	3.749	36.5	0.124	38.3	0.131	74.8	0.255	653.4	2.228	441.0	1.504
F04079	996.0	3.802	30.9	0.118	36.4	0.139	67.3	0.257	337.6	1.289	407.5	1.555
F04080	759.2	3.072	32.8	0.133	31.4	0.127	64.2	0.260	454.7	1.840	373.1	1.510
Number of females	10	10	10	10	10	10	10	10	10	10	10	10
Mean	1019.5	3.692	36.2	0.132	33.8	0.124	70.0	0.256	537.8	1.951	416.7	1.522
S.D.	206.2	0.568	3.2	0.011	3.3	0.015	5.1	0.022	156.8	0.528	36.2	0.150
Significance	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DT	KW	KW	KW	AN	KW	AN	AN	KW	AN	AN

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

NS: Not significantly different from the control group.

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

KW: Analysis by Kruskal-Wallis' test (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 2-butoxyethyl acetate in rats

Organ weight of females

High dose (BEA 500 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)
F04071	263.2	13.3	0.051	20.6	0.078	21.2	0.081	25.7	0.098	46.9	0.178
F04072	296.8	12.8	0.043	20.7	0.070	34.9	0.118	37.7	0.127	72.6	0.245
F04073	306.9	14.2	0.046	16.8	0.055	28.9	0.094	29.1	0.095	58.0	0.189
F04074	256.6	14.9	0.058	13.9	0.054	25.2	0.098	28.3	0.110	53.5	0.208
F04075	262.8	12.4	0.047	20.3	0.077	27.7	0.105	31.6	0.120	59.3	0.226
F04076	281.1	14.8	0.053	20.4	0.073	34.0	0.121	36.6	0.130	70.6	0.251
F04077	276.5	15.1	0.055	21.2	0.077	27.3	0.099	28.1	0.102	55.4	0.200
F04078	293.3	13.8	0.047	27.1	0.092	35.1	0.120	37.0	0.126	72.1	0.246
F04079	262.0	14.6	0.056	19.8	0.076	26.3	0.100	27.9	0.106	54.2	0.207
F04080	247.1	16.3	0.066	27.3	0.110	22.4	0.091	27.7	0.112	50.1	0.203
Number of females	10	10	10	10	10	10	10	10	10	10	10
Mean	274.6	14.2	0.052	20.8	0.076	28.3	0.103	31.0	0.113	59.3	0.215
S.D.	19.6	1.2	0.007	4.0	0.016	5.0	0.013	4.5	0.013	9.3	0.025
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	DT	AN	KW	AN	AN	KW	AN	AN	AN	AN

NS: Not significantly different from the control group.

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 9

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of males

Animal No.	Organs	Findings	Notes
MO1001	All organs/	Within normal limits	
MO1002	All organs/	Within normal limits	
MO1003	All organs/	Within normal limits	
MO1004	All organs/	Within normal limits	
MO1005	All organs/	Within normal limits	
MO1006	All organs/	Within normal limits	
MO1007	All organs/	Within normal limits	
MO1008	All organs/	Within normal limits	
MO1009	All organs/	Within normal limits	
MO1010	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of males

Animal No.	Organs	Findings	Notes
MO2011	All organs/	Within normal limits	
MO2012	All organs/	Within normal limits	
MO2013	All organs/	Within normal limits	
MO2014	All organs/	Within normal limits	
MO2015	All organs/	Within normal limits	
MO2016	All organs/	Within normal limits	
MO2017	All organs/	Within normal limits	
MO2018	All organs/	Within normal limits	
MO2019	All organs/	Within normal limits	
MO2020	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of males

Animal No.	Organs	Findings	Notes
M03021	Brain/ Skull/	Recessed area Elevated area	Cerebrum, Focal Cranial cavity side, Focal
M03022	All organs/	Within normal limits	
M03023	Spleen/ Stomach/	Discoloration, dark colored Thickening, mucosa	Forestomach
M03024	Spleen/	Discoloration, dark colored	
M03025	All organs/	Within normal limits	
M03026	All organs/	Within normal limits	
M03027	All organs/	Within normal limits	
M03028	All organs/	Within normal limits	
M03029	All organs/	Within normal limits	
M03030	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of males

Animal No.	Fate	Organs	Findings	Notes
M04031		Spleen/ Stomach/ Thymus/	Discoloration, dark colored Enlargement Thickening, mucosa Small	Forestomach
M04032		Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
M04033		Spleen/	Discoloration, dark colored Enlargement	
M04034		Ileum/ Kidney/ Spleen/ Stomach/	Diverticulum Pale colored area Discoloration, dark colored Enlargement Thickening, mucosa	Left Forestomach
M04035		Spleen/	Discoloration, dark colored Enlargement	
M04036	D	Cecum/ Esophagus/ External appearance/ Heart/ Lung/ Spleen/ Stomach/ Thymus/	Decrease, content Dilatation, lumen Retention, foamy fluid Soiled fur Whitish area Discoloration, dark reddish Discoloration, pale colored Small Attachment, black substance Elevated area Small	Perioral, Pericolar Scattered Mucosa, Glandular stomach Mucosa, Forestomach
M04037		Ileum/ Spleen/	Diverticulum Discoloration, dark colored Enlargement	

D: Died during the dosing period.

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of males

Animal No.	Organs	Findings	Notes
MO4037	Stomach/	Thickening, mucosa	Forestomach
MO4038	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
MO4039	Spleen/ Stomach/	Discoloration, dark colored Thickening, mucosa	Forestomach
MO4040	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of females

Animal No.	Organs	Findings	Notes
F01041	All organs/	Within normal limits	
F01042	All organs/	Within normal limits	
F01043	All organs/	Within normal limits	
F01044	All organs/	Within normal limits	
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 2-butoxyethyl acetate in rats

Macroscopic findings of females

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	All organs/	Within normal limits	
F02059	All organs/	Within normal limits	
F02060	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of females

Animal No.	Organs	Findings	Notes
F03061	All organs/	Within normal limits	
F03062	All organs/	Within normal limits	
F03063	All organs/	Within normal limits	
F03064	All organs/	Within normal limits	
F03065	All organs/	Within normal limits	
F03066	All organs/	Within normal limits	
F03067	All organs/	Within normal limits	
F03068	All organs/	Within normal limits	
F03069	All organs/	Within normal limits	
F03070	All organs/	Within normal limits	

Appendix 9 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Macroscopic findings of females

Animal No.	Organs	Findings	Notes
F04071	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
F04072	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
F04073	Spleen/	Discoloration, dark colored Enlargement	
F04074	Spleen/	Discoloration, dark colored Enlargement	
F04075	Spleen/	Discoloration, dark colored Enlargement	
F04076	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
F04077	Spleen/	Discoloration, dark colored Enlargement	
F04078	Spleen/ Stomach/	Discoloration, dark colored Enlargement Thickening, mucosa	Forestomach
F04079	Spleen/	Discoloration, dark colored Enlargement	
F04080	Spleen/	Discoloration, dark colored	

Appendix 10

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

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 /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule ± Mineralization ±	Olfactory epithelium, Respiratory epithelium Lamina propria
	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 /	Cellular infiltration, mononuclear cell ± Fibrosis, focal ±	Myocardium, Focal Myocardium
	Lung /	Accumulation, foam cell + Mineralization ±	Alveolus Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Mineralization ±	Cortex
	Spleen /	Deposit, hemosiderin ± Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Within normal limits	
	Cecum /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01001	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 /	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		
M01002	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Cyst-like lesion P	Intermediate lobe
	Eyeball /	Dysplasia, retina P	Unilateral
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule ± Mineralization ±	Olfactory epithelium Lamina propria
	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01002	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
		Fibrosis, focal ±	Myocardium
	Lung /	Accumulation, foam cell ±	Alveolus
		Mineralization ±	Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Basophilic tubule, cortex ±	
		Cellular infiltration, lymphocyte ±	Interstitial
	Spleen /	Deposit, hemosiderin ±	
		Hematopoiesis, extramedullary 2+	
	Pancreas /	Atrophy, acinar cell ±	Focal
	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 /	Cellular infiltration, lymphocyte ±	Submucosa
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 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01002	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
M01003	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	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	
	Lung /	Accumulation, foam cell \pm Mineralization \pm	Alveolus Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Basophilic tubule, cortex \pm	
	Spleen /	Deposit, hemosiderin \pm 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 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01003	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	
	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 /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule ±	Olfactory epithelium
	Zyngal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01004	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Cellular infiltration, mononuclear cell	± Myocardium, Focal
	Lung /	Granuloma +	Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+ Microgranuloma ±	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin + Hematopoiesis, extramedullary +	
	Pancreas /	Atrophy, acinar cell ±	Focal
	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 /	Within normal limits		
Marrow, sternum /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01004	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
M01005	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	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell \pm	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte \pm	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin + Hematopoiesis, extramedullary \pm	
	Pancreas /	Within normal limits	
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 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01005	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 /	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		
M01006	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization \pm	Lamina propria
	Zymbal gland /	Dilatation, cystic \pm	Duct
	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 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01006	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte \pm Microgranuloma \pm	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin \pm 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 \pm	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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01006	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 \pm	Lamina propria
	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 /	Fatty change, hepatocyte + Microgranuloma \pm	Periportal
	Kidney /	Mineralization \pm	Cortex
	Spleen /	Deposit, hemosiderin + Hematopoiesis, extramedullary +	
Pancreas /	Within normal limits		
Adrenal gland /	Within normal limits		
Stomach /	Edema, lamina propria \pm	Limiting ridge	
Duodenum /	Within normal limits		
Jejunum /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01007	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 \pm	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		
M01008	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 globule \pm Mineralization \pm	Olfactory epithelium Lamina propria
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	
	Esophagus /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01008	Trachea /	Within normal limits	
	Aorta /	Within normal limits	
	Thyroid gland /	Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
		Degeneration/necrosis, myocardial ±	Focal
		Fibrosis, focal ±	Myocardium
	Lung /	Accumulation, foam cell ±	Alveolus
		Metaplasia, osseous ±	Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 3+	Periportal
		Microgranuloma +	
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin +	
		Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01008	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	
M01009	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 /	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 /	Cellular infiltration, mononuclear cell ± Fibrosis, focal ±	Myocardium, Focal Myocardium
	Lung /	Accumulation, foam cell ± Metaplasia, osseous ±	Alveolus Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Basophilic tubule, cortex ± Hemorrhage ±	Intratubular, Focal, Cortex
Spleen /	Deposit, hemosiderin ±		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01009	Spleen /	Hematopoiesis, extramedullary +	Focal Islet
	Pancreas /	Atrophy, acinar cell \pm Fibrosis, focal \pm	
	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 \pm	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		
M01010	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Mineralization \pm	Cornea
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01010	Nasal cavity /	Eosinophilic globule +	Olfactory epithelium, Respiratory epithelium
	Zybal 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 /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
		Degeneration/necrosis, myocardial ±	Focal
	Lung /	Accumulation, foam cell ±	Alveolus
		Mineralization ±	Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Basophilic tubule, cortex ±	
		Mineralization ±	Cortex
	Spleen /	Deposit, hemosiderin +	
		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 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Organs	Findings	Notes
M01010	Prostate /	Cellular infiltration, lymphocyte \pm	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M02011	Liver / Kidney / Spleen /	Fatty change, hepatocyte ± Basophilic tubule, cortex ± Deposit, hemosiderin ± Hematopoiesis, extramedullary +	Periportal
	Stomach / Marrow, femur / Marrow, sternum /	Edema, lamina propria ± Within normal limits Within normal limits	Limiting ridge
M02012	Liver / Kidney / Spleen /	Fatty change, hepatocyte + Microgranuloma ± Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary +	Periportal
	Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Within normal limits	
M02013	Liver / Kidney / Spleen /	Fatty change, hepatocyte 2+ Basophilic tubule, cortex ± Cellular infiltration, lymphocyte ± Deposit, hemosiderin + Hematopoiesis, extramedullary +	Periportal Interstitial
	Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Within normal limits	
M02014	Liver / Kidney / Spleen /	Fatty change, hepatocyte 2+ Basophilic tubule, cortex ± Mineralization ± Deposit, hemosiderin + Hematopoiesis, extramedullary +	Periportal Cortex
	Stomach / Marrow, femur / Marrow, sternum /	Edema, lamina propria ± Within normal limits Within normal limits	Limiting ridge

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Organs	Findings	Notes
M02015	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte + Microgranuloma ± Within normal limits Deposit, hemosiderin ± Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Periportal
M02016	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte 2+ Within normal limits Deposit, hemosiderin ± Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Periportal
M02017	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte 2+ Basophilic tubule, cortex ± Mineralization ± Deposit, hemosiderin ± Hematopoiesis, extramedullary + Edema, lamina propria ± Within normal limits Within normal limits	Periportal Cortex Limiting ridge
M02018	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte 2+ Within normal limits Deposit, hemosiderin ± Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Periportal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M02019	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin + Hematopoiesis, extramedullary +	
	Stomach /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	
M02020	Liver /	Fatty change, hepatocyte 2+	Periportal
	Kidney /	Basophilic tubule, cortex ±	
	Spleen /	Deposit, hemosiderin ± Hematopoiesis, extramedullary 2+	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes	
M03021	Liver /	Fatty change, hepatocyte +	Periportal	
	Kidney /	Within normal limits		
	Spleen /	Deposit, hemosiderin +		
		Hematopoiesis, extramedullary +		
	Stomach /	Within normal limits		
	Marrow, femur /	Within normal limits		
	Marrow, sternum /	Within normal limits		
	Brain /	Cellular infiltration, mononuclear cell +		Meninx, Focal, Recessed area
		Deposit, pigment, brown ±		Meninx, Focal, Recessed area
		Thickening, meninx ±		Focal
Skull /	Thickening ±	Focal		
M03022	Liver /	Fatty change, hepatocyte ±		Periportal
	Kidney /	Within normal limits		
	Spleen /	Deposit, hemosiderin +		
		Hematopoiesis, extramedullary +	Limiting ridge	
	Stomach /	Edema, lamina propria +		
	Marrow, femur /	Within normal limits		
Marrow, sternum /	Within normal limits			
M03023	Liver /	Deposit, hemosiderin ±	Kupffer cell	
		Fatty change, hepatocyte 2+	Periportal	
		Microgranuloma ±		
	Kidney /	Basophilic tubule, cortex ±		
	Spleen /	Deposit, hemosiderin 2+		
		Hematopoiesis, extramedullary 2+		
	Stomach /	Within normal limits		
	Marrow, femur /	Hematopoiesis, increased ±		
	Marrow, sternum /	Hematopoiesis, increased ±		
	M03024	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Fatty change, hepatocyte ±	Periportal	
		Microgranuloma ±		
	Kidney /	Basophilic tubule, cortex ±		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M03024	Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Mineralization \pm Deposit, hemosiderin + Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Cortex
M03025	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte 2+ Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Periportal
M03026	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte + Mineralization \pm Deposit, hemosiderin + Hematopoiesis, extramedullary 2+ Within normal limits Within normal limits Within normal limits	Periportal Cortex
M03027	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary + Within normal limits Hematopoiesis, increased \pm Within normal limits	
M03028	Liver / Kidney / Spleen /	Fatty change, hepatocyte + Within normal limits Deposit, hemosiderin +	Periportal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Organs	Findings	Notes
M03028	Spleen / Stomach / Marrow, femur / Marrow, sternum /	Hematopoiesis, extramedullary + Edema, lamina propria ± Within normal limits Within normal limits	Limiting ridge
M03029	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte + Microgranuloma ± Within normal limits Deposit, hemosiderin 2+ Hematopoiesis, extramedullary + Edema, lamina propria ± Within normal limits Within normal limits	Periportal Limiting ridge
M03030	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte + Microgranuloma ± Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary 2+ Within normal limits Within normal limits Within normal limits	Periportal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04031	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization \pm	Lamina propria
	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 /	Atrophy \pm	
	Heart /	Within normal limits	
	Lung /	Metaplasia, osseous \pm Mineralization \pm	Focal Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin \pm Hypertrophy, hepatocyte \pm	Kupffer cell Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin \pm Mineralization \pm	Proximal tubule Papilla
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 3+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria +	Limiting ridge
	Duodenum /	Within normal limits	
Jejunum /	Within normal limits		
Ileum /	Within normal limits		
Cecum /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04031	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 /	Hematopoiesis, increased +	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	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 /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization \pm Necrosis, focal \pm	Lamina propria Olfactory epithelium, Respiratory epithelium
	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04032	Thyroid gland / Parathyroid gland / Thymus / Heart / Lung / Bronchus / Liver /	Ultimobranchial body P Within normal limits Hyperplasia, epithelial tubule/cord ± Cellular infiltration, mononuclear cell ± Metaplasia, osseous ± Within normal limits Deposit, hemosiderin + Fatty change, hepatocyte ± Hypertrophy, hepatocyte ± Tension lipidosis P	Focal Myocardium, Focal Focal Kupffer cell Periportal Centrilobular, Midzonal
	Kidney / Spleen /	Deposit, hemosiderin + Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 3+	Proximal tubule
	Pancreas / Adrenal gland / Stomach / Duodenum / Jejunum / Ileum / Cecum / Colon / Rectum / Lymph node, submandibular / Lymph node, mesenteric / Testis / Epididymis / Prostate / Seminal vesicle / Coagulating gland / Urinary bladder / Femur / Marrow, femur / Sternum / Marrow, sternum /	Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Cellular infiltration, lymphocyte + Within normal limits Within normal limits Within normal limits Within normal limits Hematopoiesis, increased + Within normal limits Hematopoiesis, increased 2+	Interstitial

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04032	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 \pm	Lamina propria
	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 /	Accumulation, foam cell \pm	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin \pm	Kupffer cell
		Fatty change, hepatocyte \pm	Periportal
		Microgranuloma +	
Kidney /	Deposit, hemosiderin \pm	Proximal tubule	
Spleen /	Deposit, hemosiderin 2+		
	Hematopoiesis, extramedullary 3+		
Pancreas /	Within normal limits		
Adrenal gland /	Within normal limits		
Stomach /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04033	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 /	Hematopoiesis, increased \pm	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04034	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 + Necrosis, focal \pm	Lamina propria Olfactory epithelium, Respiratory epithelium
	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 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04034	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 /	Cellular infiltration, mononuclear cell \pm	Myocardium, Focal
		Degeneration/necrosis, myocardial \pm	Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin +	Kupffer cell
		Fatty change, hepatocyte \pm	Periportal
		Tension lipidosis P	
	Kidney /	Deposit, hemosiderin \pm	Proximal tubule
	Spleen /	Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary 3+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Hematopoiesis, extramedullary +	Sinusoid
	Stomach /	Edema, lamina propria \pm	Limiting ridge
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Diverticulum P	
	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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04034	Femur /	Within normal limits	
	Marrow, femur /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	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	
	Eyeball /	Dysplasia, retina P	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 /	Within normal limits	
	Heart /	Cellular infiltration, mononuclear cell ± Myocardium, Focal	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ± Fatty change, hepatocyte ± Microgranuloma ±	Kupffer cell Periportal
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
Spleen /	Deposit, hemosiderin 2+		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Fate	Organs	Findings	Notes
M04035		Spleen / Pancreas / Adrenal gland / Stomach / Duodenum / Jejunum / Ileum / Cecum / Colon / Rectum / Lymph node, submandibular / Lymph node, mesenteric / Testis / Epididymis / Prostate / Seminal vesicle / Coagulating gland / Urinary bladder / Femur / Marrow, femur / Sternum / Marrow, sternum / Skeletal muscle / Sciatic nerve / Skin / Mammary gland /	Hematopoiesis, extramedullary 2+ Within normal limits Within normal limits Edema, lamina propria + Vacuolation, limiting ridge ± Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Hematopoiesis, increased + Within normal limits Hematopoiesis, increased ± Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits	Limiting ridge Epithelial layer
M04036	D	Brain / Spinal cord / Pituitary gland / Eyeball / Harderian gland / Optic nerve /	Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits Within normal limits	

D: Died during the dosing period.

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of males

Animal No.	Fate	Organs	Findings	Notes
M04036	D	Nasal cavity /	Cellular infiltration, neutrophil + Eosinophilic globule ± Necrosis, focal +	Mucosa Olfactory epithelium Olfactory epithelium, Respiratory epithelium
		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 /	Atrophy 2+	
		Heart /	Cellular infiltration, mononuclear cell ± Degeneration/necrosis, myocardial 2+ Fibrosis, focal + Mineralization +	Myocardium, Focal Perivascular, Multifocal, With mineralization Myocardium Arterial wall
		Lung /	Cellular infiltration, macrophage + Cellular infiltration, neutrophil + Edema 3+	Peribronchial Peribronchial Alveolus
		Bronchus /	Cellular infiltration, neutrophil +	Lumen
		Liver /	Deposit, hemosiderin ±	Kupffer cell
		Kidney /	Within normal limits	
		Spleen /	Atrophy 3+ Deposit, hemosiderin 3+	
		Pancreas /	Within normal limits	
		Adrenal gland /	Hypertrophy, cortical cell ±	Diffuse
		Stomach /	Ulcer +	Forestomach
		Duodenum /	Within normal limits	
		Jejunum /	Autolysis	
		Ileum /	Within normal limits	
		Cecum /	Within normal limits	
		Colon /	Within normal limits	
		Rectum /	Within normal limits	

D: Died during the dosing period.

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of males

Animal No.	Fate	Organs	Findings	Notes
M04036	D	Lymph node, submandibular /	Atrophy + Necrosis +	Lymphocyte, Diffuse
		Lymph node, mesenteric /	Within normal limits	
		Testis /	Within normal limits	
		Epididymis /	Cell debris ±	Lumen
		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 /	Cellular infiltration, macrophage 2+ Hematopoiesis, decreased 2+ Necrosis +	
		Sternum /	Within normal limits	
		Marrow, sternum /	Cellular infiltration, macrophage + Hematopoiesis, decreased 2+	
		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 globule ± Mineralization ±	Olfactory epithelium, Respiratory epithelium Lamina propria
		Zymbal gland /	Within normal limits	
		Submandibular gland /	Within normal limits	
		Sublingual gland /	Within normal limits	
		Tongue /	Within normal limits	
		Esophagus /	Within normal limits	

D: Died during the dosing period.

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04037	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 /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin + Hypertrophy, hepatocyte ±	Kupffer cell Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	Duodenum /	Within normal limits	
	Jejunum /	Within normal limits	
	Ileum /	Diverticulum P	
	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 /	Hematopoiesis, increased +	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04037	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	
	Zymal gland /	Dilatation, cystic +	Duct
	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 /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
		Degeneration/necrosis, myocardial ±	Focal
	Lung /	Accumulation, foam cell ±	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary 2+	
Pancreas /	Within normal limits		
Adrenal gland /	Within normal limits		
Stomach /	Edema, lamina propria ±	Limiting ridge	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04038	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
Skin /	Within normal limits		
Mammary gland /	Within normal limits		
M04039	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Cyst-like lesion P	Intermediate lobe
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization ±	Lamina propria
	Zymbal gland /	Within normal limits	
	Submandibular gland /	Within normal limits	
	Sublingual gland /	Within normal limits	
	Tongue /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04039	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, focal ±	Myocardium
	Lung /	Mineralization ±	Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
	Kidney /	Cellular infiltration, lymphocyte ±	Interstitial
		Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 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 /	Within normal limits	
	Epididymis /	Cellular infiltration, lymphocyte ±	Interstitial
	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 /	Hematopoiesis, increased ±		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04039	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	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 /	Cyst P	Anterior lobe
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule ± Mineralization ±	Olfactory epithelium, Respiratory epithelium Lamina propria
	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, Focal
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ± Microgranuloma +	Kupffer cell
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 2+	
Pancreas /	Atrophy, acinar cell ±	Focal	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of males

Animal No.	Organs	Findings	Notes
M04040	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria +	Limiting ridge
	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 /	Hematopoiesis, increased +	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	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 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01041	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 globule ±	Olfactory epithelium, Respiratory epithelium
	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 /	Ectopic thymic tissue P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Within normal limits	
	Heart /	Within normal limits	
	Lung /	Accumulation, foam cell ± Microgranuloma ± Mineralization ±	Alveolus Arterial wall, Focal
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Mineralization ±	Medulla
	Spleen /	Deposit, hemosiderin + 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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01041	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		
F01042	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule \pm	Olfactory epithelium
	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 /	Ectopic thymic tissue P Ultimobranchial body P	
Parathyroid gland /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01043	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	
	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	
	Thyroid gland /	Ectopic thymic tissue P Ultimobranchial body P	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial tubule/cord ±	Focal
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Within normal limits	
	Kidney /	Basophilic tubule, cortex ±	
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	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 2-butoxyethyl acetate in rats
 Histopathological findings of females

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 /	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	
F01044	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 globule +	Olfactory epithelium, Respiratory epithelium
	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 /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01044	Bronchus /	Within normal limits	
	Liver /	Within normal limits	
	Kidney /	Cellular infiltration, lymphocyte \pm Hyperplasia, transitional cell \pm Mineralization +	Interstitial Renal pelvis. With inflammatory cell infiltration Medulla
	Spleen /	Deposit, hemosiderin + Hematopoiesis, extramedullary \pm	
	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		
F01045	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01045	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Mineralization \pm	Lamina propria
	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 /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte \pm	Periportal
	Kidney /	Basophilic tubule, cortex \pm	
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary \pm	
	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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01045	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	
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 /	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 /	Hyperplasia, epithelial tubule/cord ±	Focal
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
Liver /	Fatty change, hepatocyte +	Periportal	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01046	Kidney /	Basophilic tubule, cortex \pm	Medulla
	Spleen /	Mineralization \pm Deposit, hemosiderin + Hematopoiesis, extramedullary +	
	Pancreas /	Within normal limits	Limiting ridge
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria \pm	
	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	
	Eyeball /	Within normal limits	
	Harderian gland /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01047	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zybal 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, Focal
	Bronchus /	Within normal limits	
	Liver /	Microgranuloma ± Tension lipidosis P	
	Kidney /	Basophilic tubule, cortex ± Cellular infiltration, lymphocyte ± Cyst P Mineralization ±	Around the cyst Interstitial, Around the cyst Cortex, Medulla Medulla
	Spleen /	Deposit, hemosiderin 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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01047	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	
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 /	Within normal limits	
	Zybal 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 tubule/cord ±	Focal
	Heart /	Within normal limits	
	Lung /	Within normal limits	
Bronchus /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes	
F01048	Liver /	Microgranuloma ±	Medulla	
	Kidney /	Mineralization ±		
	Spleen /	Deposit, hemosiderin 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 /	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			
F01049	Brain /	Within normal limits		
	Spinal cord /	Within normal limits		
	Pituitary gland /	Within normal limits		
	Eyeball /	Within normal limits		
	Harderian gland /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01049	Optic nerve /	Within normal limits	
	Nasal cavity /	Within normal limits	
	Zybal 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 /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Fatty change, hepatocyte \pm	Periportal
	Kidney /	Cellular infiltration, lymphocyte \pm	Interstitial
		Mineralization \pm	Medulla
	Spleen /	Deposit, hemosiderin 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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01049	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 /	Within normal limits	
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule ±	Olfactory epithelium
	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 /	Fatty change, hepatocyte ±	Periportal	
Kidney /	Within normal limits		
Spleen /	Deposit, hemosiderin +		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F01050	Spleen /	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 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F02051	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary ± Edema, lamina propria ± Within normal limits Within normal limits	Limiting ridge
F02052	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte ± Microgranuloma ± Mineralization ± Deposit, hemosiderin 2+ Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Periportal Medulla
F02053	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Deposit, hemosiderin + Hematopoiesis, extramedullary ± Edema, lamina propria + Within normal limits Within normal limits	Limiting ridge
F02054	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte ± Mineralization + Deposit, hemosiderin 2+ Hematopoiesis, extramedullary + Edema, lamina propria ± Within normal limits Within normal limits	Periportal Medulla Limiting ridge
F02055	Liver /	Fatty change, hepatocyte ±	Periportal

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F02055	Kidney /	Basophilic tubule, cortex ±	Medulla
	Spleen /	Mineralization ±	
	Stomach /	Deposit, hemosiderin 2+	Limiting ridge
	Marrow, femur /	Hematopoiesis, extramedullary +	
Marrow, sternum /	Edema, lamina propria ±	Within normal limits	
F02056	Liver /	Within normal limits	Medulla
	Kidney /	Basophilic tubule, cortex ±	
	Spleen /	Mineralization +	
	Stomach /	Deposit, hemosiderin 2+	
Marrow, femur /	Hematopoiesis, extramedullary ±	Within normal limits	
Marrow, sternum /	Within normal limits	Within normal limits	
F02057	Liver /	Within normal limits	Medulla
	Kidney /	Basophilic tubule, cortex ±	
	Spleen /	Mineralization ±	
	Stomach /	Deposit, hemosiderin +	
Marrow, femur /	Hematopoiesis, extramedullary ±	Within normal limits	
Marrow, sternum /	Within normal limits	Within normal limits	
F02058	Liver /	Fatty change, hepatocyte ±	Periportal
	Kidney /	Basophilic tubule, cortex ±	Interstitial
		Cellular infiltration, lymphocyte ±	
		Cyst P	Medulla
	Mineralization ±	Medulla	
Spleen /	Deposit, hemosiderin 2+		
Stomach /	Hematopoiesis, extramedullary ±		
Marrow, femur /	Within normal limits		
	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F02058	Marrow, sternum /	Within normal limits	
F02059	Liver / Kidney / Spleen /	Within normal limits Within normal limits Deposit, hemosiderin 2+ Hematopoiesis, extramedullary ±	
	Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Within normal limits	
F02060	Liver / Kidney / Spleen /	Fatty change, hepatocyte ± Microgranuloma ± Hyperplasia, transitional cell ± Deposit, hemosiderin + Hematopoiesis, extramedullary +	Periportal Renal pelvis, With inflammatory cell infiltration
	Stomach / Marrow, femur / Marrow, sternum /	Within normal limits Within normal limits Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F03061	Liver /	Deposit, hemosiderin \pm	Kupffer cell
	Kidney /	Microgranuloma +	Medulla
	Spleen /	Mineralization \pm	
		Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary +	
F03062	Stomach /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	
	Liver /	Fatty change, hepatocyte \pm	Periportal
	Kidney /	Deposit, hemosiderin \pm	Proximal tubule
F03063	Spleen /	Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary +	
	Stomach /	Edema, lamina propria +	Limiting ridge
	Marrow, femur /	Hematopoiesis, increased \pm	
	Marrow, sternum /	Within normal limits	
F03064	Liver /	Microgranuloma \pm	
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin +	
		Hematopoiesis, extramedullary +	
		Edema, lamina propria \pm	Limiting ridge
F03064	Marrow, femur /	Hematopoiesis, increased \pm	
	Marrow, sternum /	Within normal limits	
	Liver /	Deposit, hemosiderin \pm	Kupffer cell
		Fatty change, hepatocyte \pm	Periportal
		Hypertrophy, hepatocyte \pm	Centrilobular, Midzonal
F03064		Microgranuloma \pm	
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary +	
	Stomach /	Within normal limits	
	Marrow, femur /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F03064	Marrow, sternum /	Within normal limits	
F03065	Liver /	Deposit, hemosiderin ± Fatty change, hepatocyte ± Microgranuloma ±	Kupffer cell Periportal
	Kidney /	Basophilic tubule, cortex ±	
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 2+	
	Stomach /	Edema, lamina propria +	Limiting ridge
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	
F03066	Liver /	Fatty change, hepatocyte ± Tension lipidosis P	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary +	
	Stomach /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	
F03067	Liver /	Fatty change, hepatocyte ± Microgranuloma ±	Periportal
	Kidney /	Within normal limits	
	Spleen /	Deposit, hemosiderin 2+ Hematopoiesis, extramedullary +	
	Stomach /	Within normal limits	
	Marrow, femur /	Within normal limits	
	Marrow, sternum /	Within normal limits	
F03068	Liver /	Deposit, hemosiderin ± Fatty change, hepatocyte ± Hypertrophy, hepatocyte ±	Kupffer cell Periportal Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin ±	Proximal tubule

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F03068	Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Mineralization ± Deposit, hemosiderin 2+ Hematopoiesis, extramedullary + Within normal limits Within normal limits Within normal limits	Medulla
F03069	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Deposit, hemosiderin ± Fatty change, hepatocyte ± Basophilic tubule, cortex ± Cellular infiltration, lymphocyte ± Deposit, hemosiderin 2+ Hematopoiesis, extramedullary 2+ Within normal limits Within normal limits Within normal limits	Kupffer cell Periportal Interstitial
F03070	Liver / Kidney / Spleen / Stomach / Marrow, femur / Marrow, sternum /	Fatty change, hepatocyte ± Hypertrophy, hepatocyte ± Deposit, hemosiderin ± Deposit, hemosiderin 2+ Hematopoiesis, extramedullary + Edema, lamina propria + Hematopoiesis, increased + Hematopoiesis, increased ±	Periportal Centrilobular, Midzonal Proximal tubule Limiting ridge

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

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 /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Eosinophilic globule \pm	Olfactory epithelium
	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 /	Deposit, hemosiderin + Hypertrophy, hepatocyte \pm Microgranuloma \pm	Kupffer cell Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin \pm	Proximal tubule
	Spleen /	Deposit, hemosiderin 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		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04071	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased +	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
Mammary gland /	Within normal limits		
F04072	Brain /	Within normal limits	
	Spinal cord /	Within normal limits	
	Pituitary gland /	Within normal limits	
	Eyeball /	Within normal limits	
	Harderian gland /	Cellular infiltration, lymphocyte \pm	Interstitial
	Optic nerve /	Within normal limits	
	Nasal cavity /	Cellular infiltration, neutrophil \pm Necrosis, focal \pm	Mucosa Olfactory epithelium, Respiratory epithelium
	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04072	Thymus /	Hyperplasia, epithelial tubule/cord ±	Focal
	Heart /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin +	Kupffer cell
		Fatty change, hepatocyte ±	Periportal
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
		Microgranuloma ±	
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 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	
	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	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 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04072	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 /	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	
	Lung /	Accumulation, foam cell ±	Alveolus
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin +	Kupffer cell
		Fatty change, hepatocyte ±	Periportal
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin +	Proximal tubule
		Mineralization ±	Medulla
	Spleen /	Deposit, hemosiderin 3+	
		Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	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 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04073	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	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 /	Eosinophilic globule ±	Olfactory epithelium, Respiratory epithelium
	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04074	Thyroid gland /	Within normal limits	
	Parathyroid gland /	Within normal limits	
	Thymus /	Hyperplasia, epithelial tubule/cord ±	Focal
	Heart /	Within normal limits	
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin +	Kupffer cell
		Fatty change, hepatocyte ±	Periportal
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
		Microgranuloma ±	
	Kidney /	Deposit, hemosiderin +	Proximal tubule
	Spleen /	Deposit, hemosiderin 2+	
		Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria ±	Limiting ridge
	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 /	Hematopoiesis, increased 2+		
Sternum /	Within normal limits		
Marrow, sternum /	Hematopoiesis, increased 2+		
Skeletal muscle /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04075	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 /	Mineralization \pm	Interstitial gland
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	
	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	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 /	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	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04076	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 /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Fatty change, hepatocyte ±	Periportal
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
		Microgranuloma +	
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 3+	
		Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria +	Limiting ridge
	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 /	Hematopoiesis, increased 2+		
Sternum /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04077	Spleen /	Hematopoiesis, extramedullary 2+	
	Pancreas /	Within normal limits	
	Adrenal gland /	Within normal limits	
	Stomach /	Edema, lamina propria +	Limiting ridge
	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
F04078	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	
	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 globule ±	Olfactory epithelium	
Zymbal gland /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04078	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 tubule/cord ±	Focal
	Heart /	Cellular infiltration, mononuclear cell ±	Myocardium, Focal
	Lung /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Hypertrophy, hepatocyte ±	Gentrilobular, Midzonal
		Microgranuloma ±	
	Kidney /	Deposit, hemosiderin ±	Proximal tubule
	Spleen /	Deposit, hemosiderin 3+	
		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	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
Uterus /	Within normal limits		
Vagina /	Within normal limits		
Urinary bladder /	Within normal limits		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04078	Femur /	Within normal limits	
	Marrow, femur /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
F04079	Mammary gland /	Within normal limits	
	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 \pm	Lamina propria
	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 tubule/cord \pm	Focal
	Heart /	Within normal limits	
	Lung /	Mineralization \pm	Arterial wall, Focal
Bronchus /	Within normal limits		
Liver /	Deposit, hemosiderin +	Kupffer cell	
	Fatty change, hepatocyte \pm	Periportal	
	Hypertrophy, hepatocyte \pm	Centrilobular, Midzonal	
	Deposit, hemosiderin \pm	Proximal tubule	
	Deposit, hemosiderin 2+		

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04079	Spleen /	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 /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
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 /	Cellular infiltration, neutrophil ±	Mucosa
		Mineralization ±	Lamina propria

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats
 Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04080	Nasal cavity /	Necrosis, focal +	Olfactory epithelium, Respiratory epithelium
	Zybal 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 /	Within normal limits	
	Bronchus /	Within normal limits	
	Liver /	Deposit, hemosiderin ±	Kupffer cell
		Fatty change, hepatocyte ±	Periportal
		Hypertrophy, hepatocyte ±	Centrilobular, Midzonal
	Kidney /	Deposit, hemosiderin +	Proximal tubule
	Spleen /	Deposit, hemosiderin 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	
	Ovary /	Within normal limits	
	Oviduct /	Within normal limits	
	Uterus /	Within normal limits	

Appendix 10 (Continued)

Ninety-day repeated dose oral toxicity test of 2-butoxyethyl acetate in rats

Histopathological findings of females

Animal No.	Organs	Findings	Notes
F04080	Vagina /	Within normal limits	
	Urinary bladder /	Within normal limits	
	Femur /	Within normal limits	
	Marrow, femur /	Hematopoiesis, increased 2+	
	Sternum /	Within normal limits	
	Marrow, sternum /	Hematopoiesis, increased 2+	
	Skeletal muscle /	Within normal limits	
	Sciatic nerve /	Within normal limits	
	Skin /	Within normal limits	
	Mammary gland /	Within normal limits	

試験番号 : XXXXXXXXXX

含量試験結果 (1/2)

被験物質 : 2-butoxyethyl acetate

調製年月日 : XXXXXXXXXXロット番号 : XXXXXXXXXX測定年月日 : XXXXXXXXXX

媒 体 : トウモロコシ油

試料番号	調製濃度(A) (mg/mL)	測定濃度(B) (mg/mL)	平均測定濃度(C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
1	5.00	5.14	5.04	102.8	100.9	102.0
2		5.00		100.0		99.2
3		4.99		99.8		99.0
4	25.0	24.7	24.7	98.8	98.9	100.0
5		24.4		97.6		98.8
6		25.1		100.4		101.6
7	125	122	120	97.6	96.3	101.7
8		121		96.8		100.8
9		118		94.4		98.3

含量の判定基準 (溶液検体)

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

試験番号 : XXXXXXXXXX

含量試験結果 (2/2)

被験物質 : 2-butoxyethyl acetate

調製年月日 : XXXXXXXXXXロット番号 : XXXXXXXXXX測定年月日 : XXXXXXXXXX

媒体 : トウモロコシ油

試料番号	調製濃度(A) (mg/mL)	測定濃度(B) (mg/mL)	平均測定濃度(C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
10	5.00	5.10	5.04	102.0	100.9	101.2
11		4.94		98.8		98.0
12		5.09		101.8		101.0
13	25.0	24.8	24.6	99.2	98.5	100.8
14		24.4		97.6		99.2
15		24.7		98.8		100.4
16	125	124	125	99.2	100.0	99.2
17		126		100.8		100.8
18		125		100.0		100.0

含量の判定基準 (溶液検体)

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

Annex 3

投与検体中の被験物質濃度測定法

1. 試薬

2-プロパノール (HPLC 用、以下、2-PrOH)	和光純薬工業
1,2-ジクロロベンゼン (東京化成特級)	東京化成工業

2. 機器

電子天秤 (R200D)	ザルトリウス
電子天秤 (MSA1203S100DE)	ザルトリウス
ガスクロマトグラフ	島津製作所
構成 : GC-17A (ガスクロマトグラフ)、AOC-20i (オートインジェクタ)、C-R7A (データ処理装置)	

3. 試験方法

特に規定のない限り、試験操作は室温 (1~30°C) で行った。

3.1 標準溶液の調製

被験物質約 50 mg を精密に量り、2-PrOH に溶かして正確に 50 mL とした。

この液 1 mL を正確に採り、2-PrOH を加えて正確に 50 mL とし標準原液 (約 20 $\mu\text{g/mL}$) とした。

標準原液を 1, 2 および 5 mL ずつ正確に採り、それぞれ IS 溶液 1 mL を正確に加え、さらに 2-PrOH を加えて正確に 20 mL とし、標準溶液 1~3 (約 1, 2 および 5 $\mu\text{g/mL}$ 、St 1~3) とした。標準原液および標準溶液は、測定日ごと、 $n=1$ で調製した。

3.2 IS 溶液の調製

1,2-ジクロロベンゼン 5 mg を量り、2-PrOH に溶かして正確に 100 mL とし、IS 溶液 (約 50 $\mu\text{g/mL}$) とした。IS 溶液は、測定日ごと、 $n=1$ で調製した。

3.3 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 $n=3$ で調製した。

1) 125 mg/mL 溶液

投与検体 1 mL を正確に採り、2-PrOH を加えて正確に 50 mL とした。

この液 1 mL を正確に採り、2-PrOH を加えて正確に 50 mL とした。

さらにこの液 1 mL を正確に採り、IS 溶液 1 mL を加え、2-PrOH で正確に 20 mL とした (約 2.5 $\mu\text{g/mL}$ 、希釈率 50000)。

2) 25 mg/mL 溶液

投与検体 1 mL を正確に採り、2-PrOH を加えて正確に 50 mL とした。

この液 1 mL を正確に採り、2-PrOH を加えて正確に 10 mL とした。

さらにこの液 1 mL を正確に採り、IS 溶液 1 mL を加え、2-PrOH で正確に 20 mL とした (約 2.5 $\mu\text{g/mL}$ 、希釈率 10000)。

3) 5 mg/mL 溶液

投与検体 1 mL を正確に採り、2-PrOH を加えて正確に 100 mL とした。

この液 1 mL を正確に採り、IS 溶液 1 mL を加え、2-PrOH で正確に 20 mL とした (約 2.5 $\mu\text{g/mL}$ 、希釈率 2000)。

3.4 被験物質の濃度測定

標準溶液 (St 1~3) および試料溶液につき、それぞれ下記の試験条件でガスクロマトグラフィーにより試験を行った。標準溶液および試料溶液をそれぞれ 1 回ずつ測定し、標準溶液から作成した検量線 (内標法による) 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、初回の含量試験において、投与検体の媒体確認用溶液 (注 1) を 1 回測定し、被験物質に相当するピークがないことを確認した。

なお、濃度測定法については、事前に「媒体中の 2-butoxyethyl acetate 濃度測定法バリデーション」(試験番号 Q-16-021、GLP 適用外) を実施し問題がないことを確認した。

Annex 3 (Continued)

注1：媒体 1 mL を採り、2-PrOH を加えて正確に 100 mL とした。
この液 1 mL を正確に採り、2-PrOH で正確に 20 mL とした（希釈率 2000）。

試験条件

検出器	水素炎イオン化検出器 (FID)
カラム	Rtx-624 (内径 0.32 mm、長さ 30 m、膜厚 1.8 μ m、Restek)
キャリアガス	ヘリウム (100 kPa)
カラム温度	
標準溶液	50°C (0 min)、15°C/min、200°C (0 min)
試料溶液	50°C (0 min)、15°C/min、240°C (5 min)
各種温度	注入口：250°C、検出器：280°C、試料：室温
試料注入方式	スプリットレス (サンプリング時間：0.5 min)
注入量	1 μ L
ピークモニター時間	10 min
システム適合性	測定開始前に溶媒 (2-PrOH) および IS 溶液 (1 \rightarrow 20 \cdot 溶媒) をそれぞれ 1 回測定し、クロマトグラム上の BEA の保持時間付近に妨害ピークがないことを確認した。測定開始前および測定終了後に標準溶液 (St 2) を 3 回および 1 回測定し、測定開始前初回測定の BEA および IS の保持時間と測定終了後の保持時間の変動を確認した。また、測定開始前 n=3 測定のピーク面積比の平均値と相対標準偏差およびピーク面積比の平均値に対する測定終了後のピーク面積比の変動を確認した。相対標準偏差および変動の許容基準は相対標準偏差が 5.0%以内、保持時間の差がそれぞれ \pm 0.5 分以内、ピーク面積比の偏差 (%) が \pm 5.0%以内を目安とした。

3.5 数値の取り扱い

- 1) 標準原液および標準溶液の濃度は、切り捨てて有効数字 4 桁で表示した。
- 2) 投与検体中の濃度およびその平均は、四捨五入して有効数字 3 桁で表示した。
- 3) 含量 (%)、平均含量 (%) およびばらつき (%) は、四捨五入して小数第 1 位まで表示した。
- 4) 保持時間およびピーク面積は、データ処理装置の出力値をそのまま用いた。
- 5) システム適合性におけるピーク面積比 (平均値を含む) は、四捨五入して有効数字 6 桁で、保持時間の差 (分) およびピーク面積比の偏差 (%) は、四捨五入して小数第 1 位まで表示した。