

最終報告書

4-isopropylbenzaldehyde のラットを用いる 反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

試験施設

一般財団法人食品薬品安全センター 秦野

〒257-8523 神奈川県秦野市落合 729 番地の

TEL 0463-82-4751

試験委託者 厚生労働省医薬食品局審査管理課 化学物質安全対策室
(東京都千代田区霞が関 1-2-2)

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被験物質 4-isopropylbenzaldehyde

試験項目 反復投与毒性ならびに生殖発生毒性試験

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試験資料保管場所 秦野研究所資料保存室

被験物質保管場所 秦野研究所被験物質保存庫

保管期間 試験終了後 10 年間
その後の保管については試験委託者と協議する。

運営管理者 一般財団法人食品薬品安全センター 秦野研究所
所長 

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

2014 年 3 月 13 日

試験責任者 

試験従事者

試験責任者

試験担当主任者

試験担当者

投与・観察

動物飼育管理

(検疫を含む)

尿検査

血液学検査

(採血を含む)

血液生化学検査

病理学検査

被験物質管理

検体調製

化学分析

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信頼性保証書

要約

4-Isopropylbenzaldehyde の反復投与毒性・生殖発生毒性併合試験を化審法ガイドラインに従って実施した。被験物質をトウモロコシ油で希釈して 0、30、100 ならびに 300 mg/kg の用量で、各群とも雌雄各 12 匹の Crl:CD (SD) ラットに強制経口投与した。なお、投与 18 日までに 300 mg/kg 群の雌 4 匹が死亡したことから、投与 19 日から 300 mg/kg 群の投与量は 150 mg/kg (以下、300/150 mg/kg 群) に変更した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および妊娠期間を通して哺育 4 日までの 42～45 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。ただし、100 mg/kg 以上の群では、妊娠動物が得られなかったことから、妊娠以降の検査対象は 30 mg/kg 群のみとなった。0 および 300/150 mg/kg 群は非交配雌 (10 匹/群) を設け、42 日間投与した後に半数を剖検し、残りの半数と 0、100 および 300/150 mg/kg 群の雄 5 匹は、42 日間投与した後に 14 日間飼育して剖検した。

1. 反復投与毒性および回復性

300/150 mg/kg 群の交配雌 4 例と非交配雌 4 例が死亡または瀕死状態となった。死亡例では、生存時に自発運動の低下、排便量の減少、痩せなどが観察され、同群の生存雌においても同様の症状が観察された。雄では死亡例および一般状態の異常は観察されなかった。体重増加抑制は 300/150 mg/kg 群の雄および非交配雌でみられ、30 mg/kg 群の分娩雌では、哺育 4 日の体重が減少した。摂餌量の低下は 100 mg/kg 以上の群の雄と 300/150 mg/kg 群の交配雌および非交配雌で認められた。自発運動測定では、立ち上がり回数の減少が 300/150 mg/kg 群の雄にみられた。

尿検査では、尿量の増加、尿比重の低下、カリウムおよび塩素イオン濃度の低下が 300/150 mg/kg 群の非交配雌で認められた。血液学検査では MCHC と血小板数の低下が 300/150 mg/kg 群の非交配雌、血小板数の低下傾向が 100 mg/kg 以上の群の不妊雌にみられた。血液生化学検査では、総蛋白、総コレステロールおよびカルシウム濃度の低下と AST、尿素窒素および無機リン濃度の上昇が 300/150 mg/kg 群の雄で、アルブミンおよびカルシウム濃度の低下が 300/150 mg/kg 群の非交配雌および 100 mg/kg 以上の群の不妊雌で、グルコース濃度の増加が 30 mg/kg 群の分娩雌でみられた。

剖検では、胸腺の重量低下が 30 mg/kg 以上の群の雄で、肝臓の重量増加が 30 mg/kg 群の分娩雌、100 mg/kg 以上の群の雄および不妊雌、さらには 300/150 mg/kg 群の非交配雌でみられた。腎臓の相対重量の増加は 300/150 mg/kg 群の雄および非交配雌、さらには 100 mg/kg 以上の群の不妊雌でみられた。その他、精巣の相対重量が 300/150 mg/kg 群で低下し、精巣上体の相対重量が 100 mg/kg 群で増加した。病理組織学検査では、死亡または瀕死動物に、肝細胞の空胞変性、核の大小不同を伴うびまん性の肝細胞肥大、腸間膜リンパ節の萎縮、脾臓の赤脾髄および白脾髄領域の減少、腎臓の遠位尿細管あるいは集合管の空胞変性、胸腺の萎縮などが観察された。生存例においても、肝臓では核の大小不同を伴うびまん性の肝細胞肥大が 100 mg/kg 以上の群の雄および不妊雌、さらには 300/150 mg/kg 群の非交配雌に、小肉芽腫の頻度増加と単細胞壊死が 100 mg/kg 以上の群の雄および 300/150 mg/kg 群の不妊雌にみられ、腎臓では遠位尿細管あるいは集合管の空胞変性が 300/150 mg/kg 群の非交配雌および不妊雌で

認められた。精巣では、両側性に精細管の萎縮、伸長精子細胞の減少、ライディッヒ細胞の過形成、精細管内の多核巨細胞が 300/150 mg/kg 群で観察され、精巣上体では、管腔内精子数の減少、管腔内細胞残屑および尾部の精子肉芽腫が 100 mg/kg 以上の群で観察された。

回復観察では、体重増加の抑制が 100 mg/kg 以上の群の雄および 300/150 mg/kg 群の非交配雌にみられ、血中総蛋白濃度の低下と胸腺重量の増加が 300/150 mg/kg 群の非交配雌に、精巣および精巣上体の重量低下が 300/150 mg/kg 群の雄にみられた。病理組織学検査では、核の大小不同を伴うびまん性の肝細胞肥大が 100 mg/kg 以上の群の雄、精細管の萎縮、伸長精子細胞の減少、ライディッヒ細胞の過形成および多核巨細胞が 300/150 mg/kg 群の雄、管腔内精子数の減少および管腔内細胞残屑が 100 mg/kg 以上の群の雄で観察された。

2. 生殖発生毒性

性周期に被験物質の影響は認められず、交尾は全例で確認されたが、100 mg/kg 以上の群の雌は全例が不妊であった。無処置雌との再交配においても、100 mg/kg 以上の群の雄は全例で交尾が確認されたが、妊孕性は確認されなかった。

30 mg/kg 群の妊娠期間および出産率、分娩状態、哺育状態、黄体数、着床数および着床率に被験物質投与の影響は認められなかった。また、30 mg/kg 群の出生児についても、生存率および形態に被験物質の影響は認められなかったが、哺育 0 日の雌児の体重が低下した。

3. 無毒性量

30 mg/kg 群では、胸腺重量の低下が雄で、肝臓重量の増加とグルコース濃度の増加が分娩雌でみられたことから雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 30 mg/kg/day 未満と判断された。また、30 mg/kg 群では、分娩雌の哺育 4 日の体重が減少し、哺育 0 日の雌児の体重が低下したことから生殖発生毒性に対する無毒性量も 30 mg/kg/day 未満と判断された。

試験目的

雌雄ラットの交配前(2週間)および交配期間中(最長2週間)、ならびに雄では交配期間終了後2週間、雌では妊娠期間を通して周産期(哺育4日まで)に4-isopropylbenzaldehydeを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインと GLP

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

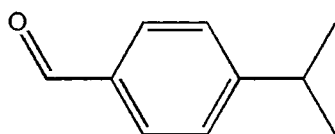
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和48年10月1日法律第105号、平成24年9月5日一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成18年4月28日、環境省告示第88号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成18年6月1日、科発第0601001号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成2年10月1日、平成22年10月1日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120184A)。なお、余剰動物うち雌10匹は本試験の再交配に使用したが(動物実験承認番号:3120015A)、それ以外に承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質である4-isopropylbenzaldehyde(別名:クミンアルデヒド、CAS No. 122-03-2、分子式: $C_{10}H_{12}O$ 、分子量:148.20、性状:不快臭を有する無色澄明の液体、沸点:約235℃(初留点)、密度:0.978 g/mL(20℃)、ロット番号:KWE2088、含量:99.6%(毛管カラム GC)、Annex A、以下、4-IBA)は、XXXXXXXXXXより購入し(被験物質入手:2012年7月3日)、使用時まで室温(実測値20.1～28.1℃)、遮光、密閉で保管した。4-IBAの構造式を次に示す。



被験物質の安定性は、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、スペクトルに変化がなかったことが確認されている(試験番号 G-12-005)。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8 週齢の Sprague-Dawley (SD) 系 [CrI:CD(SD)、SPF] ラット雄 55 匹、雌 83 匹を購入し、飼育室(15 号室)に収容した。入荷日も含めて 15 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に赤のフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 3 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2012 年 9 月 10 日
入荷時体重	:雄 250.9~280.6 g、雌 176.6~212.0 g
検疫終了日	:2012 年 9 月 24 日
検疫終了時体重	:雄 328.1~422.7 g、雌 224.4~294.7 g

検疫・馴化期間中の一般状態、詳細な症状観察および体重推移に試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物では、規則的な性周期の回帰が認められない 10 匹を除外し、検疫終了時の体重に基づく体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とした。余剰動物のうち、雄動物は他の目的へ転用し、雌動物 10 匹は本試験の再交配に供し、残りの雌動物 5 匹は安楽死させた。

動物は許容温度 21.0~25.0℃、許容湿度 40.0~75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時~19 時)点灯、12 時間(19 時~7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(剖検前の絶食に関しては剖検の項を参照)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に 1 匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 23.0~25.5℃、湿度は 43.5~74.5%であった。また、供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを

確認した。

3. 投与検体

1) 調製

被験物質を秤量し、媒体(トウモロコシ油、製造元:ナカライテスク、製造番号:V2K9025)を加え攪拌混和させ、7.5 w/v%液を調製した。さらに 7.5 w/v%液を媒体によって希釈し、2.5 ならびに 0.75 w/v%液を段階的に調製した。なお、投与 19 日から高用量群に用いた 3.75 w/v%液は被験物質を秤量し、媒体を加え攪拌混和させ調製した。調製した検体は室温・遮光下(実測値 23.0～25.5℃)で保管し、安定性の保証期間内に使用した。

2) 安定性試験

投与に先立ち、0.75 および 7.5 w/v%(7.5 および 75 mg/mL)濃度の調製検体について、室温、遮光条件下における 8 日間の安定性を確認した(Annex B)。調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

3) 含量試験

初回に調製した投与検体(0.75、2.5、7.5 w/v%および 3.75 w/v%)について、被験物質含量を測定した。その結果、平均含量は調製指示濃度の 100.7～102.7%であり、各測定値のばらつきはそれぞれ平均値の 97.8～101.8%で規定範囲内にあった(Annex D-1、D-2)。調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「4-isopropylbenzaldehyde 別名クミンアルデヒドのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号 R-12-001)の結果をもとに設定した。なお、予備試験で使用した被験物質および媒体は本試験と同じロットを用いた。

予備試験では、0(媒体、トウモロコシ油)、100、300 および 1000 mg/kg の 4-IBA を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した結果、1000 mg/kg 群においては雌雄とも全例が投与 4 日までに死亡または瀕死状態となった。100 および 300 mg/kg 群においては、死亡例および重篤な症状は観察されなかったが、雌の体重増加が抑制された。また、両群では用量依存的な肝臓重量の増加と、胃粘膜面の肥厚が観察された。血液生化学検査では、100 および 300 mg/kg 群において AST、ALT、LDH および胆汁酸濃度が用量依存的に増加する傾向がみられた。

従って、高用量には毒性影響を生じさせるが死亡や重度の苦痛を引き起こさないと考えられる 300 mg/kg を、中用量には用量相関性を明確にする 100 mg/kg を設定し、低用量には無毒性量(NOAEL)が得られると期待される 30 mg/kg を設定した。なお、本試験では投与 18 日までに 300 mg/kg 群の雌 4 匹が死亡したことから、投与 19 日から 300 mg/kg 群の投与量は 150 mg/kg(以下、300/150 mg/kg 群)に変更した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物

は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 42～45 回)、分娩しない雌は剖検前日(妊娠 26 日相当日)まで、非交配雌の反復毒性を評価するために設定したサテライト群は投与 42 日まで、1 日 1 回、1 週 7 回、毎日 9 時～13 時の間(9 時 01 分～12 時 12 分)に投与した。投与容量は 4 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体であるトウモロコシ油を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	トウモロコシ油 (媒体)	0	0	4	M01001～M01012*	F01001～F01012
低用量群	4-IBA	30	0.75	4	M02013～M02024	F02013～F02024
中用量群	4-IBA	100	2.5	4	M03025～M03036*	F03025～F03036
高用量群	4-IBA	300/150#	7.5/3.75#	4	M04037～M04048*	F04037～F04048
対照群 (サテライト群)	トウモロコシ油 (媒体)	0	0	4	-	F05049～F05058*
高用量群 (サテライト群)	4-IBA	300/150#	7.5/3.75#	4	-	F06059～F06068*

#: 投与 19 日から投与量を 300 mg/kg から 150 mg/kg、濃度を 7.5 w/v% から 3.75 w/v% に変更した。

*: 雄の対照群、中用量および高用量群と雌の対照群(サテライト群)については動物番号の大きい 5 例を、雌の高用量群(サテライト群)については動物番号の大きい 3 例を回復観察に供した。

5. 検査法

1) 親動物(F₀)

①一般状態の観察

全例について、飼育期間中は毎日 1 回、投与期間中は投与前後の毎日 2 回以上観察した。症状が発現した場合、速やかな回復が期待されない所見を除き、症状が発現している間、断続的に、可能な限り観察を継続した。

②回復および遅発毒性の観察

雄動物は対照群、中用量および高用量群のうち動物番号の大きい各 5 例を、雌動物はサテライト群の動物番号の大きい 5 例(高用量群は 3 例)を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、一般状態を観察した。

③詳細な症状観察

全例について、検疫終了日、投与 8、15、24、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間)、回復期間中は回復 7 および 14 日にスコアリング法による詳細な症状観察を行った。観察は、いずれも 13 時～17 時の間(13 時 04 分～16 時 25 分)に行った。

まず、ケージ越しでの観察を行い、ケージから取り出す際に外表を観察し、作業台上での観察を行った。作業台上では、体位、姿勢、探索行動、立毛、眼裂、振戦、痙攣、呼吸数、歩行、常同行動、奇妙な行動、挙尾反応、

身づくろい、発声、排尿、排便、接触に対する反応、撤去反射、耳介反射を観察した。

④機能検査

各群の動物番号の若い雄 5 例とサテライト群の動物番号の若い 5 例(高用量群は 3 例)については、投与 39 日に自発運動測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩例については投与期間が近接し、出来るだけ分娩から日数が経過した各群の 5 例を選び、投与最終週に自発運動測定、握力測定および刺激に対する感覚運動反応を検査した。なお、投与最終週に実施した自発運動測定で被験物質投与の影響が示唆された雄動物については、回復 11 日にも自発運動測定を実施した。

(1) 刺激に対する感覚運動反応

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

(2) 握力測定

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

(3) 自発運動測定

自発運動量測定装置(SUPER-MEX、室町機械)を用いて、20 分間の自発運動量(区画移動数および立ち上がり回数)を計測し、計測値は 5 分毎に集計した。試験対象動物は、検査直前に別室の装置設置場所に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物のサテライト群は、投与 1、4、7、14、21、28、35、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、4、7、14 日、妊娠 0(交尾確認日)、7、14、20 日、哺育 0、4 日および剖検日に測定した。

⑥摂餌量測定

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

⑦尿検査

雄および雌動物のサテライト群を検査対象とし、投与 37 日の検査では各群の動物番号が若い 5 例、また、回復 13 日における検査では回復観察に供した全例を検査した。

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

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

⑧性周期観察

全例の雌について、検疫 3 日から性周期を観察し、群分け後、投与開始以降も引き続きサテライト群を除く全例の膣スミア標本を作製し、各動物の同居後、交尾が確認されるまで性周期を観察した。また、群ごとの平均発情回帰日数(個体ごとの発情期から発情期までの日数の平均)および投与開始後に 4 あるいは 5 日間隔の性周期がそれ以外の性周期に変化した動物の頻度を群毎に算出した。なお、規則的に 4～5 日の間で性周期が回帰している動物を正常と判断した。

⑨交配

投与 15 日の 16 時 21 分より同群内の雌雄を 1 対 1 で同居させた。翌朝より毎朝、膣栓を確認し、同居中の雌の膣スミア標本を作製して鏡検した。膣内に膣栓あるいは膣スミア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率[(交尾動物数/交配に用いた動物数)×100, %]、妊娠率[(妊娠動物数/交尾した雌動物数)×100, %]を算出した。

投与 42 日の 16 時 30 分より中用量および高用量の回復観察に供した雄動物と試験に使用しなかった余剰雌動物を再交配させた。交尾が確認された雌動物は、妊娠 13 日相当日に剖検して生存胎児の有無を確認した。

⑩妊娠・分娩・哺育状態の観察

交尾雌は全例を自然分娩させた。分娩の確認は、妊娠 21 日相当日から分娩が確認されるまで毎日、午前と午後に行い、15 時までには分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかった動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1～4 日の間、毎日観察した。分娩例については、妊娠期間(妊娠 0 日から分娩日までの日数)を求めた。また、剖検時には、妊娠黄体数と着床数を数え、着床率[(着床数/妊娠黄体数)×100, %]を算出した。

⑪採血

雄の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日における剖検では回復観察に供した全例について採血を行った。分娩雌の投与終了時剖検では、投与期間が近接した各群の 5 例につ

いて採血を行った。なお、中用量および高用量群については、投与の影響により分娩例が得られなかったことから、未分娩例の各 5 例について採血を行った。サテライト群の投与終了時剖検では各群の動物番号が若い 5 例(高用量群は 3 例)、回復 15 日における剖検では回復観察に供した全例について採血を行った。いずれも解剖前 18～24 時間絶食させた後、腹部後大静脈から以下の(1)、(2)、(3)の順に注射筒を換えて採血した。

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

⑫血液学検査

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

項目	測定法	使用機器
赤血球数(RBC)	電気抵抗検出法	血液自動分析装置 XT-2000iV(シスメックス)
白血球数(WBC)	半導体レーザを用いたフローサイトメトリー法	同上
白血球分類	同上	同上
網状赤血球比率(RET%)	同上	同上
血色素量(HGB)	SLSヘモグロビン法	同上
平均赤血球容積(MCV)	計算($HCT \times 1000 / RBC$)	同上
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
平均赤血球血色素量(MCH)	計算($HGB \times 1000 / RBC$)	同上
平均赤血球血色素濃度(MCHC)	計算($HGB \times 100 / HCT$)	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-1000(シスメックス)
プロトロンビン時間(PT)	同上	同上

⑬血液生化学検査

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

項目	測定法	使用機器
総蛋白濃度(TP)	ビュレット法	自動分析装置 JCA-BM6010(日本電子)
アルブミン濃度(rALB)	BCG法	同上
グルコース濃度(Glc)	ヘキソキナーゼ・G-6-PDH法	同上
総コレステロール濃度(TC)	コレステロールオキシダーゼ・HMMPs法	同上
トリグリセリド濃度(TG)	GPO・HMMPs法、グリセリン消去法	同上
リン脂質濃度(PL)	コリンオキシダーゼ・DAOS法	同上

項目	測定法	使用機器
尿素窒素濃度 (BUN)	ウレアーゼ・G6PDH法,ウレアーゼ律速系	自動分析装置 JCA-BM6010(日本電子)
クレアチニン濃度 (cre)	Jaffé法	同上
γ-グルタミルトランスペプチダーゼ活性 (γ-GTP)	IFCC法	同上
アルカリフォスファターゼ活性 (ALP)	GSCC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)	同上	同上
乳酸脱水素酵素活性 (LDH)	JSCC標準化対応法	同上
カルシウム濃度 (Ca)	OCPC法	同上
総ビリルビン濃度 (tbil)	酵素法	同上
無機リン濃度 (IP)	モリブデン酸直接法	同上
胆汁酸濃度 (TBA)	酵素サイクリング法	同上
A/G比	計算 (rALB/(TP- rALB))	同上
ナトリウムイオン濃度 (Na)	イオン電極法	全自動電解質分析装置 EA05(エイアントイー)
カリウムイオン濃度 (K)	同上	同上
塩素イオン濃度 (Cl)	同上	同上

⑭剖検および器官重量

以下の時期に、採血対象動物はペントバルビタールナトリウム麻酔下で採血した後、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させ、引き続き剖検した。死亡動物は死亡確認日に剖検した。

対象動物	解剖時期	屠殺前の絶食
雄		
投与終了時剖検例	投与 42 日の翌日	18～24 時間絶食
回復観察例	回復 15 日	18～24 時間絶食
雌		
分娩例	哺育 4 日の翌日	18～24 時間絶食
交尾したが分娩しなかった例(未分娩)	妊娠 27 日相当日	18～24 時間絶食
サテライト群(投与終了時剖検例)	投与 42 日の翌日	18～24 時間絶食
サテライト群(回復観察例)	回復 15 日	18～24 時間絶食
全哺育児が死亡した例	全哺育児が死亡した日	実施せず
瀕死動物	試験責任者が決定	実施せず
死亡動物	死亡確認日	実施せず

死亡動物以外の全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精囊(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精囊および凝固腺、卵巣、子宮、膈、膀胱、大腿骨および大腿骨骨髓、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。

死亡動物以外の肺および気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶

液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、全哺育児が死亡した例および瀕死動物の器官重量値は評価対象から除外した。

⑮病理組織学検査

剖検した動物のうち、雄の投与終了時剖検では対照群ならびに 300/150 mg/kg 群の動物番号が若い各 5 例、雌の投与終了時剖検では、採血を行った対照群ならびに 30 mg/kg 群の分娩雌各 5 例と 300/150 mg/kg 群の未分娩雌 5 例について、組織学検査対象器官(保存した器官・組織のうち乳腺は除く)のヘマトキシリン・エオジン(HE)標本を作製し、病理組織学検査を実施した。

死亡動物および瀕死動物についても同様に、病理組織学検査を実施した。また、剖検時に異常がみられた器官・組織に関しても同様に HE 標本を作製し、病理組織学検査を実施した。

なお、投与期間終了時の剖検例で被験物質投与の影響が示唆された器官・組織については、低および中用量群の各 5 例と回復期間終了時の剖検例についても病理組織学検査を実施した。

2) 出生児(F₁)

①出生児の観察

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

②剖検

死亡児は外表奇形の有無を観察して剖検し、10%中性緩衝ホルマリン溶液に固定して保存した。生存児は哺育 4 日に外表奇形の有無を観察してセボフルラン吸入麻酔下に放血致死させて剖検し、内部器官の異常の有無を観察した。

6. データの解析法

性周期の変化した動物の頻度、交尾率、受胎率については Fisher の直接確率検定を行った(有意水準:5%)。被験物質投与群の病理組織学検査所見のうち、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の間の有意差検定を行った(有意水準:5%)。

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差

が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一意性について検定(有意水準:5%)を行った。分散が一意であった場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一意でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

予見することができなか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

2012 年 10 月 4 日、11:00～14:26 に受変電設備の定期点検のために停電し、それに伴い動物飼育室内の照明が明期に消え、同日の 11:00～14:30 に空調が停止した。また、復電後に一過性の温度上昇(16:30～16:45、最高温度 25.5℃)が観測された。しかし、いずれの動物の一般状態にも上述事象に起因したと考えられる変化は認められず、温度の上昇はわずかで短時間であったことから、試験への影響はないと判断した。

2012 年 10 月 26 日、10:21～10:37(16 分間)、14:15～14:16(1 分間)および 16:02～16:07(5 分間)に本館電灯用回路が停電し、本館の動物飼育室内の照明が消えた。しかし、いずれの動物の一般状態等に上述事象に起因したと考えられる変化は認められず、消灯は短時間であったことから、試験への影響はないと判断した。

齧歯類自発運動量測定法の標準操作手順書には、「測定用ケージへの動物の収容は、乱数表を用いて、無作為に実施する」と記載されていたが、試験では乱数表を用いず、動物番号の若い順に測定用ケージへ収容した。しかし、各測定用ケージの精度管理(センサー感度)の測定値を確認し、装置間のばらつきはないと判断されたことから、試験成績へ影響はないと判断した。

その他、「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。

試験成績

1. 親動物

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

投与期間中の雄(Table 1-1)では、30 mg/kg 群の雄 1 例(動物番号 M02016)に歯の欠損が投与 33 日に発見され、排便量減少が投与 33 日から 35 日まで継続して観察されたが、その他の雄動物に一般状態の異常はみられなかった。

回復期間中の雄 (Table 1-2) では、一般状態の異常は観察されなかった。

投与期間中の交配雌 (Table 2-1, Table 3) では、投与 14 日から投与 28 日の間に死亡動物が 300/150 mg/kg 群の 4 例 (動物番号 F04041, F04042, F04043, F04046) にみられた。これらの例では自発運動の低下、鎮静、排便量の減少、うずくまり、立毛、痩せ、衰弱、歩行異常、被毛の汚れ、体温下降が観察された (下表参照)。同群、交配雌の生存例においても自発運動の低下あるいは鎮静が 4 例で観察されたほか、排便量減少が 2 例、一過性の痩せが 1 例、皮膚のびらんが 1 例に観察された。

投与期間中の非交配雌 (Table 2-2) では、投与 8 日から投与 23 日の間に死亡または瀕死動物が 300/150 mg/kg 群の 4 例 (動物番号 F06059, F06063, F06064, F06068) にみられた。これらの例では自発運動の低下、鎮静、排便量の減少、うずくまり、立毛、痩せ、赤色尿、歩行異常、被毛の汚れが観察された (下表参照)。同群、非交配雌の生存例においても自発運動低下あるいは鎮静が 2 例で観察されたほか、排便量減少が 1 例に観察された。

回復観察中の非交配雌 (Table 2-3) では、一般状態の異常は観察されなかった。

対照群および 30 mg/kg 群の妊娠雌では、妊娠期間中 (Table 3) および哺育期間中 (Table 4) に、一般状態の異常は観察されなかった。

動物番号	死亡/瀕死	剖検日	死亡までの症状
交配雌			
F04041	死亡	投与 17 日	衰弱 (投与 16 日)。
F04042	死亡	投与 14 日	自発運動低下または鎮静 (投与 4, 5 日)。自発運動低下、口の周囲汚れ、および下腹部汚れ (投与 13 日)。
F04043	死亡	妊娠 7 日相当日 (投与 23 日)	自発運動低下または鎮静 (投与 3, 4 日)。立毛、痩せ、排便量減少、歩行異常、うずくまり、または下腹部汚れ (投与 18~22 日)。
F04046	死亡	妊娠 11 日相当日 (投与 28 日)	歩行異常、うずくまり、痩せ、立毛、体温下降、鼻周囲汚れ (妊娠 11 日相当日)。
非交配雌			
F06059	死亡	投与 18 日	自発運動低下または鎮静 (投与 3, 4 日)。排便量減少および立毛 (投与 17 日)。
F06063	瀕死	投与 23 日	自発運動低下 (投与 3, 6 日)。痩せ、排便量減少、立毛、下腹部汚れ、赤色尿、うずくまり、または歩行異常 (投与 18~23 日)。
F06064	死亡	投与 8 日	自発運動低下または鎮静 (投与 3, 4, 6 日)。被毛汚れ、うずくまり、痩せ、自発運動低下、下腹部汚れ、および赤色尿 (投与 7 日)。
F06068	死亡	投与 19 日	自発運動低下または鎮静 (投与 4, 6 日)。痩せ、下腹部汚れ、または排便量減少 (投与 7 日~13 日)。排便量減少、立毛、うずくまり、または赤色尿 (投与 17, 18 日)。

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

雌雄の詳細な症状観察では、投与期間ならびに回復期間を通して、被験物質投与の影響を示唆する変化は認められなかった。

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

投与期間中の雄 (Table 7-1) では 300/150 mg/kg 群の投与 14、21、35 および 42 日の体重が対照群と比較して有意に低下した。

回復期間中の雄 (Table 7-2) では、100 および 300/150 mg/kg 群ともに回復 1、7 および 14 日の体重が対照群と比較して有意に低下したが、再交配による体重への影響も考えられた。

投与期間中の交配雌 (Table 8-1) では体重に有意差は認められなかったが、非交配雌 (Table 8-2) では 300/150 mg/kg 群の投与 4、7、14 および 21 日の体重が対照群と比較して有意に低下した。

回復期間中の非交配雌 (Table 8-3) では、300/150 mg/kg 群の回復 1 および 7 日の体重が有意に低下した。

妊娠期間中の体重 (Table 9) には、対照群と 30 mg/kg 群との間で有意差は認められなかった。

哺育期間中の体重 (Table 10) は、30 mg/kg 群の哺育 4 日の体重が哺育 0 日の体重より減少したが、対照群と比較して有意差はなかった。

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

投与期間中の雄 (Table 11-1) では 100 および 300/150 mg/kg 群の投与 1～2 日の摂餌量が、対照群と比較して有意に低下した。

回復期間中の雄 (Table 11-2) の摂餌量には、対照群と 100 および 300/150 mg/kg 群との間に有意差は認められなかった。

投与期間中の交配雌 (Table 12-1) では 300/150 mg/kg 群の投与 1～2 日の摂餌量が対照群と比較して有意に低下した。

投与期間中の非交配雌 (Table 12-2) においても、300/150 mg/kg 群の投与 1～2 日の摂餌量が対照群と比較して有意に低下した。

回復期間中の非交配雌 (Table 12-3) の摂餌量には、対照群と 300/150 mg/kg 群との間に有意差は認められなかった。

妊娠期間中 (Table 13) および哺育期間中 (Table 14) の摂餌量には、対照群と 30 mg/kg 群との間に有意差は認められなかった。

5) 機能検査

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

投与最終週に実施したブライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼(瞬目)反射、正向反射の検査では、サテライト群を含む雌雄いずれの群の検査対象動物においても異常は認められなかった。

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

投与最終週に実施した雄の握力測定では、被験物質の影響は認められなかった。また、投与最終週に実施した分娩雌およびサテライト群の握力測定でも、被験物質の影響は認められなかった。

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

投与期間中の雄 (Table 20-1) では、300/150 mg/kg 群の開始 15 分の立ち上がり回数が対照群と比較して有意に減少した。

回復期間中の雄 (Table 20-2) では、対照群と比較して有意差は認められなかった。

投与期間中の分娩雌 (Table 21) および非交配雌 (Table 22) では、区画移動数および立ち上がり回数に被験物質投与の影響は認められなかった。

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

投与期間中の雄 (Table 23-1) では、100 mg/kg 群でナトリウムイオンの排泄量が対照群と比較して有意に増加したが、用量に依存した変化ではなかった。その他、300/150 mg/kg 群の 1 例に潜血がみられ、沈渣中に赤血球が確認されたが、その他の雄に潜血および沈渣中の赤血球は観察されなかった。

回復期間中の雄 (Table 23-2) では、100 mg/kg 群の 1 例に潜血および沈渣中の赤血球がみられたが、その他に被験物質投与の影響を示唆する変化は観察されなかった。

投与期間中の非交配雌 (Table 24-1) では、300/150 mg/kg 群の尿量が対照群に比べて有意に増加し、尿比重、尿中のカリウムイオン濃度および塩素イオン濃度がいずれも対照群と比較して有意に低下したが、各電解質の排泄量には対照群と 300/150 mg/kg 群との間で有意差はなかった。

回復期間中の非交配雌 (Table 24-2) では、300/150 mg/kg 群の 1 例で潜血と沈渣中に赤血球が確認されたが、その他に被験物質投与の影響を示唆する変化は認められなかった。

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

①雄動物

投与期間終了時の雄 (Table 25-1) では、いずれの検査項目においても被験物質投与の影響を示唆する有意な変化は認められなかった。

回復期間終了時の雄 (Table 25-2) では、100 mg/kg 群の活性化部分トロンボプラスチン時間が対照群と比較して有意に短縮したが、用量に依存した変化ではなかった。

②雌動物

投与期間終了時の分娩雌 (Table 26-1-1) では、30 mg/kg 群の好中球比率が対照群と比較して有意に増加し、リンパ球比率が有意に低下したが、同群の白血球数には対照群と比較して有意差はなかった。

100 および 300/150 mg/kg 群の不妊雌 (Table 26-1-2) では、血小板数が低下傾向を示した。

投与期間終了時の非交配雌 (Table 26-2) では、300/150 mg/kg 群の MCHC と血小板数が対照群と比較して有意に低下したが、その他の項目に被験物質投与の影響を示唆する変化は認められなかった。

回復期間終了時の非交配雌 (Table 26-3) では、対照群と 300/150 mg/kg 群との間で、被験物質投与の影響を示唆する変化は認められなかった。

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

①雄動物

投与期間終了時の雄 (Table 27-1) では、300/150 mg/kg 群の総蛋白濃度および総コレステロール濃度が対照群と比較して有意に低下し、AST および尿素窒素濃度が有意に増加した。その他、同群では無機リン濃度が対照群と比較して有意に増加し、カルシウム濃度が有意に低下した。

回復期間終了時の雄 (Table 27-2) では、100 mg/kg 群のカルシウム濃度が対照群と比較して有意に低下したが、用量に依存した変化ではなかった。

②雌動物

投与期間終了時の分娩雌 (Table 28-1-1) では、30 mg/kg 群のグルコース濃度 (平均 140 mg/dL) が対照群と比較して有意に増加し、背景データ (下表参照) の範囲を上回った。

分娩雌 (投与終了時)	試験数*	サンプル数	平均	平均±2SD
グルコース濃度	6	30	120.2	103.5-136.8

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群 (媒体: トウモロコシ油) を使用

100 および 300/150 mg/kg 群の不妊雌 (Table 28-1-2) では、後述する 300/150 mg/kg 群の非交配雌と同様、アルブミン濃度とカルシウム濃度が低下傾向を示した。

投与期間終了時の非交配雌 (Table 28-2) では、300/150 mg/kg 群のアルブミン濃度とカルシウム濃度が対照群と比較して有意に低下した。

回復期間終了時の非交配雌 (Table 28-3) では、300/150 mg/kg 群の総蛋白濃度 (平均 5.6 g/dL) が対照群と比較して有意に低下したが、その他の項目に有意な変化はなかった。

非交配雌 (回復終了時)	試験数*	サンプル数	平均	平均±2SD
総蛋白濃度	6	30	6.1	6.0-6.2

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群 (媒体: トウモロコシ油) を使用

9) 器官重量

①雄動物 (Table 29-1～29-2, Appendix 29-1～29-2)

投与期間終了時の雄 (Table 29-1) では、胸腺の絶対重量および相対重量が 30 mg/kg 以上の群で対照群と比較して有意に低下した。肝臓の絶対重量および相対重量は、100 mg/kg 以上の群で対照群と比較して有意に増加した。その他、腎臓の相対重量が 300/150 mg/kg 群で対照群と比較して有意に増加した。雄の生殖器では、精巣の相対重量が 300/150 mg/kg 群で有意に低下し、精巣上体の相対重量は 100 mg/kg 群で有意に増加した。

回復期間終了時の雄 (Table 29-2) では、心臓の絶対重量が 100 mg/kg 以上の群で、脳、腎臓および脾臓の絶対重量が 300/150 mg/kg 群で対照群と比較して有意に低下したが、いずれの器官とも相対重

量には対照群と比較して有意差はなく、体重の低下に伴う変化と考えられた。雄の生殖器では、精巣の絶対および相対重量と精巣上体の絶対重量が 300/150 mg/kg 群で有意に低下した。精囊の相対重量が 100 mg/kg 群で有意に増加したが用量に依存した変化ではなかった。

②雌動物 (Table 30-1～30-3, Appendix 30-1～30-3)

投与期間終了時の分娩雌 (Table 30-1-1) では、30 mg/kg 群の肝臓の絶対および相対重量が対照群と比較して有意に増加したが、その他の器官重量に被験物質の影響を示唆する変化は認められなかった。

不妊雌 (Table 30-1-2) では、後述する 300/150 mg/kg 群の非交配雌と同様、100 および 300/150 mg/kg 群で肝臓の絶対および相対重量と腎臓の相対重量が増加傾向を示した他、両群の卵巣重量が低下傾向を示した。

投与期間終了時の非交配雌 (Table 30-2) では、肝臓の絶対および相対重量と腎臓の相対重量が 300/150 mg/kg 群で対照群と比較して有意に増加した。その他、300/150 mg/kg 群で脳の絶対重量が有意に低下し、副腎の絶対重量が有意に増加した。

回復期間終了時の非交配雌 (Table 30-3) では、300/150 mg/kg 群で胸腺の絶対 (平均 353.2 mg) および相対重量 (平均 1.374 mg/g) が対照群と比較して有意に増加し、背景データ (下表参照) の範囲を上回った。その他、甲状腺の絶対重量 (平均 13.7 mg) が有意に低下したが、背景データの範囲 (下表参照) 内の変化であった。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
胸腺の絶対重量	6	30	246.7	199.9-293.5
胸腺の相対重量	6	30	0.827	0.716-0.937
甲状腺の絶対重量	6	30	15.9	10.6-21.1

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群 (媒体: トウモロコシ油) を使用

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

①雄の投与終了時剖検例 (Table 31-1)

投与 42 日の翌日に剖検した雄動物、対照群 7 例、30 mg/kg 群 12 例、100 mg/kg 群 7 例および 300/150 mg/kg 群 7 例の剖検所見は以下の通りである。

甲状腺では、大型化が 300/150 mg/kg 群の 1 例にみられた。

肝臓では、大型化が 30、100 および 300/150 mg/kg 群でそれぞれ 1 例、3 例および 6 例に認められ、300/150 mg/kg 群の 2 例では淡色化を伴っていた。

腎臓では、大型化が 300/150 mg/kg 群の 1 例にみられた。

脾臓では、大型化が 100 mg/kg 群および 300/150 mg/kg 群でそれぞれ 1 例にみられた。

精巣では、両側性の小型化が 300/150 mg/kg 群の 7 例 (全例) にみられ、そのうちの 5 例は水腫様であったが、同様の変化は、対照群の 1 例にも認められた。その他、両側性の大型化が 30 および

100 mg/kg 群の各 1 例にみられた。

精巣上体では、両側性の小型化が 300/150 mg/kg 群の 3 例に、大型化が 100 および 300/150 mg/kg 群の各 1 例にみられた。その他、尾部の白色結節が 100 mg/kg 群の 2 例と 300/150 mg/kg 群の 1 例にみられた。

その他の器官には、被験物質投与の影響を示唆する変化は認められなかった。

②雄の回復観察例 (Table 31-2)

回復 15 日に剖検した雄動物、対照群 5 例、100 mg/kg 群 5 例および 300/150 mg/kg 群 5 例の剖検所見は以下の通りである

精巣では、両側性の小型化が 300/150 mg/kg 群の 5 例(全例)にみられ、そのうちの 3 例は水腫様であった。

精巣上体では、両側性の小型化が 300/150 mg/kg 群の 4 例にみられ、うち 1 例は水腫様であった。また、尾部の白色(または黄白色)結節が 100 mg/kg 群の 2 例にみられた。

その他の器官には、被験物質投与の影響を示唆する所見は観察されなかった。

③雌の死亡動物および瀕死動物 (Table 32-1-1)

死亡動物として剖検した 300/150 mg/kg 群の交配雌 4 例と非交配雌 3 例および瀕死動物として剖検した非交配雌 1 例(動物番号 F06063)の剖検所見は以下の通りである。

下垂体では暗色が非交配雌の死亡動物 1 例に、甲状腺では暗色化が交配雌 1 例および非交配雌の死亡動物 1 例にみられた。

胸腺では、小型化が交配雌 3 例と非交配雌の死亡動物 2 例および瀕死動物 1 例に、暗赤色が交配雌 2 例にみられた。

肺では、暗赤色域が交配雌および非交配雌の死亡動物各 2 例に、暗赤色が交配雌 1 例にみられた。

肝臓では、大型化が交配群および非交配群の各 4 例(全例)、そのうち交配群 1 例および非交配群の死亡動物 2 例で淡色化が、交配群の 1 例で小葉像明瞭および淡色斑がみられた。

胃では、腺胃粘膜の菲薄化が交配雌 1 例にみられた。

小腸では、黄白色液の充満が非交配群の死亡動物 1 例、暗色物貯留が非交配雌の死亡動物 2 例にみられた。

腎臓では、両側性の大型化が交配雌の 1 例および非交配雌の瀕死動物 1 例、乳頭部の暗赤色が交配雌 1 例、暗色域が非交配雌の死亡動物 1 例、表面粗造が非交配雌の死亡動物 1 例にそれぞれみられた。

脾臓では、小型化が交配雌および非交配雌の各 4 例(全例)、そのうち交配雌 1 例および非交配雌の死亡動物 2 例に淡色化がみられた。

副腎では、両側性の大型化が交配雌 4 例と非交配雌の死亡動物 1 例および瀕死動物 1 例にみられた。

子宮では、暗色が交配雌 1 例にみられた。

その他、被毛の汚れが交配雌 2 例と非交配雌の死亡動物 2 例に観察された。

④分娩雌の投与終了時剖検例 (Table 32-1-2)

哺育 4 日の翌日に剖検した雌動物、対照群 11 例および 30 mg/kg 群 9 例の剖検所見は以下の通りである。

30 mg/kg 群の 2 例に胸腺の小型化がみられ、そのうちの 1 例に腺胃粘膜の暗赤色点が認められたが、それ以外に被験物質投与の影響を示唆する所見は観察されなかった。

⑤不妊例 (Table 32-1-3) および全哺育児が死亡した例 (Appendix 32-1)

妊娠 27 日相当日に剖検した不妊例、対照群 1 例、30 mg/kg 群 2 例、100 mg/kg 群 12 例、300/150 mg/kg 群 8 例および全哺育児が死亡した 30 mg/kg 群の 1 例の剖検所見は以下の通りである。

不妊例では、肝臓の大型化が 100 および 300/150 mg/kg 群でそれぞれ 3 例および 8 例 (全例)、肝臓の小葉像明瞭が 100 および 300/150 mg/kg 群でそれぞれ 1 例および 6 例、肝臓の淡色化が 100 および 300/150 mg/kg 群でそれぞれ 3 例および 4 例に観察された。その他、腺胃粘膜の暗色点/域が 100 および 300/150 mg/kg 群でそれぞれ 4 例および 1 例、前胃粘膜の浮腫が 300/150 mg/kg 群で 2 例、腺胃粘膜の陥凹部が 100 mg/kg 群の 1 例に観察された。

全哺育児が死亡した例 (動物番号 F02017) では、副腎の大型化、胸腺の小型化、前胃粘膜の浮腫、肝臓の大型化および淡色化が観察された。

⑥サテライト群の投与終了時剖検例 (Table 32-2)

投与 42 日の翌日に剖検した非交配雌、対照群 5 例および 300/150 mg/kg 群 3 例の剖検所見は以下の通りである。

肝臓では、大型化が 300/150 mg/kg 群の 3 例にみられ、そのうちの 1 例に淡色化が観察された。

胃では、腺胃粘膜の暗色点および前胃粘膜の浮腫が 300/150 mg/kg 群でそれぞれ 1 例に認められた。

⑦サテライト群の回復観察例 (Table 32-3)

回復 15 日に剖検した非交配雌、対照群 5 例および 300/150 mg/kg 群 3 例については、被験物質投与の影響を示唆する変化は観察されなかった。

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

①雄の投与終了時剖検例 (Table 33-1, Appendix 33-1)

投与終了時剖検例のうち、対照群および 300/150 mg/kg 群の 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された肝臓、脾臓、精巣および精巣上体については、30 および 100 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

甲状腺では、300/150 mg/kg 群の 1 例に鰓嚢遺残が観察されたが、対照群の 1 例にもみられた所見であった。

心臓では、300/150 mg/kg 群の 1 例に限局性の心筋の変性／線維化が観察されたが、対照群の 2 例にもみられたごく軽度な変化であった。

肺では、300/150 mg/kg 群の 2 例に肺胞内に泡沫細胞の集簇が観察されたが、対照群の 3 例にもみられたごく軽度な変化であった。

肝臓では、核の大小不同を伴うびまん性の肝細胞肥大が 100 および 300/150 mg/kg 群で認められ、その頻度および程度が対照群と比較して有意に増加した。小肉芽腫は対照群を含む各投与群でみられ、100 mg/kg 以上の群で頻度が、300/150 mg/kg 群で程度が有意に増加した。また、単細胞壊死が、100 および 300/150 mg/kg 群で認められ、100 mg/kg 群で頻度が有意に増加した。門脈周囲性に肝細胞の脂肪化が対照群を含む各投与群で観察されたが、頻度および程度に差はなかった。その他、漿膜下に限局性の壊死が 300/150 mg/kg 群の 1 例にみられたが、ごく軽度なものであった。

脾臓では、対照群を含む各群の全例に髄外造血および褐色色素の沈着が観察されたが、対照群と各投与群との間で程度の差はなかった。

腎臓では、皮質の好塩基性尿細管と髄質の鉍質沈着が 300/150 mg/kg 群でそれぞれ 1 例に観察されたが、対照群にもみられたごく軽度な変化であった。

精巣では、300/150 mg/kg 群で精細管の伸長精子細胞の減少が両側性みられ、頻度および程度ともに対照群と比較して有意に増加した。また、同群では精細管の限局性萎縮、間質にライディッヒ細胞の過形成および精細管に多核巨細胞 (Photo 1) が両側性にみられ、頻度が対照群と比較して有意に増加した。

精巣上体では、管腔内精子数の減少が 100 および 300/150 mg/kg 群で両側性にみられ、頻度および程度が対照群と比較して有意に増加した。また、管腔内細胞残屑は 100 mg/kg 以上の群で頻度が、300/150 mg/kg 群で頻度および程度が対照群と比較して有意に増加した。その他、尾部の精子肉芽腫が 100 および 300/150 mg/kg 群で観察されたが頻度および程度に有意差は認められなかった。

前立腺では、300/150 mg/kg 群の 4 例で間質のリンパ球浸潤が観察されたが、対照群の 3 例にもみられたごく軽度な変化であった。

その他の器官に被験物質投与の影響を示唆する変化は認められなかった。

②雄の回復観察例 (Table 33-2, Appendix 33-2)

回復 15 日に剖検した対照群、100 および 300/150 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が示唆された肝臓、脾臓、精巣および精巣上体について病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、核の大小不同を伴うびまん性の肝細胞の肥大が 100 mg/kg 群の 1 例および 300/150 mg/kg 群の 5 例に認められ、300/150 mg/kg 群の頻度および程度が対照群と比較して有意に増加した。門脈周囲性の肝細胞の脂肪化は、300/150 mg/kg 群で有意に減少した。その他、漿膜下の限局性壊死が 300/150 mg/kg 群の 1 例にみられたが、ごく軽度なものであった。

脾臓では、対照群、100 および 300/150 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、群間における程度の差はなかった。

精巣では、精細管の限局性萎縮、精細管の伸長精子細胞の減少および間質のライディッヒ細胞の過形成が 300/150 mg/kg 群の 5 例 (全例) で観察され、その頻度および程度が対照群と比較して有意に増加

した。また、300/150 mg/kg 群の 4 例で精細管の多核巨細胞が認められ、その頻度が対照群と比較して有意に増加した。

精巣上体では、管腔内の細胞残屑と精子数の減少が 100 mg/kg 群および 300/150 mg/kg 群の 5 例(全例)に観察され、頻度および程度が対照群と比較して有意に増加した。また、尾部の精子肉芽腫が 100 mg/kg 群の 2 例に観察された。

③雌の死亡および瀕死動物 (Table 34-1-1, Appendix 34-1, 34-2)

死亡あるいは瀕死動物として剖検した 300/150 mg/kg 群の交配雌 4 例と非交配雌の死亡動物 3 例および瀕死動物 1 例について病理組織学検査を実施した。

顎下腺では動脈周囲にリンパ球浸潤が交配雌 1 例にみられたが、ごく軽度な変化であった。

顎下リンパ節では、萎縮が交配雌 2 例と非交配雌の死亡動物 1 例および瀕死動物 1 例に観察された。

甲状腺では、異所性の胸腺組織が交配雌 2 例に認められたが、被験物質投与とは関連のない所見と考えられた。

胸腺では、萎縮が交配雌 2 例と非交配雌の死亡動物 2 例および瀕死動物 1 例にみられた。

心臓では、限局性の心筋の変性／線維化が交配雌 1 例および非交配雌の死亡動物 2 例に観察されたが、対照群の雄にもみられたごく軽度な変化であった。

肺では、肺泡内に泡沫細胞の集簇が交配雌 3 例および非交配雌の死亡動物 2 例に、動脈壁に限局性の鉍質沈着が交配雌の死亡動物 1 例に観察された。

肝臓では、肝細胞の空胞変性と核の大小不同を伴うびまん性の肝細胞の肥大が全例に認められた。その他、門脈周囲性に肝細胞の脂肪化が非交配雌の死亡動物 1 例、小肉芽腫が非交配雌の瀕死動物 1 例で観察された。

腸間膜リンパ節では、萎縮が交配雌の 3 例と非交配雌の死亡動物 2 例および瀕死動物 1 例に観察された。

脾臓では、赤脾髄領域および白脾髄領域の減少が全例に観察された。その他、褐色色素の沈着が全例、髓外造血が交配雌 1 例と非交配雌の死亡動物 2 例および瀕死動物 1 例に観察されたが、いずれも対照群の分娩雌や非交配雌にみられた変化であった。

腎臓では、遠位尿細管あるいは集合管の空胞変性が全例で観察された。その他、皮質の好塩基性尿細管と皮髄境界部の鉍質沈着が交配雌の各 1 例、乳頭部の壊死が交配雌 1 例および非交配雌の瀕死動物 1 例に観察された。

副腎では、皮質の束状帯細胞の肥大が交配雌 4 例と非交配雌の死亡動物 2 例および瀕死動物 1 例に観察された。

骨髄では、中等度の造血減少が非交配雌の死亡動物 1 例にみられた。

④分娩例の投与終了時剖検例 (Table 34-1-2, Appendix 34-1)

哺育 4 日の翌日に剖検した対照群および 30 mg/kg 群の 5 例について、病理組織検査を実施した。

胸腺では軽度の萎縮が 30 mg/kg 群の 2 例に認められた。

肺では 30 mg/kg 群の 1 例に肺泡内泡沫細胞の集簇が認められたが、対照群の 2 例にもみられたごく軽度な変化であった。

肝臓では 30 mg/kg 群の 3 例に門脈周囲性の肝細胞の脂肪化が認められた他、小肉芽腫が 30 mg/kg 群の 1 例にみられたが、両者とも対照群の雄にもみられた所見であった。

脾臓では対照群および 30 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、程度の差はなかった。

腎臓では、30 mg/kg 群の 1 例に皮髄境界部の限局性の鉍質沈着が認められたが、対照群の 1 例にもみられたごく軽度な変化であった。

⑤不妊例および全哺育児が死亡した例 (Table 34-1-3, Appendix 34-1)

不妊例は、300/150 mg/kg 群の 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された肝臓および脾臓については 100 mg/kg 群の不妊例についても病理組織学検査を実施した。その他、剖検時に異常がみられた不妊例の器官についても病理組織検査を実施した。病理組織所見は、以下の通りである。

甲状腺では 300/150 mg/kg 群の 2 例に嚢嚢遺残が、心臓では同群の 1 例に心筋の変性／線維化が観察されたが、いずれも対照群の分娩例にもみられた変化であった。

肺では 300/150 mg/kg 群の 3 例に肺胞内泡沫細胞の集簇が、同群の 1 例に動脈壁の限局性鉍質沈着が観察されたが、いずれもごく軽度な変化であった。

肝臓では、門脈周囲性の肝細胞の脂肪化が 100 mg/kg 群および 300/150 mg/kg 群の各 8 例に、核の大小不同を伴うびまん性の肝細胞の肥大が 100 mg/kg 群の 9 例および 300/150 mg/kg 群の 8 例に認められた。その他、肝臓の小肉芽腫が 100 mg/kg 群の 1 例および 300/150 mg/kg 群の 7 例、肝臓の単細胞壊死が 300/150 mg/kg 群の 6 例に認められた。

胃では、剖検時に異常がみられた 100 mg/kg 群の 2 例に前胃粘膜のびらんが認められた。

脾臓では、褐色色素沈着と髄外造血が観察した全例に認められたが、対照群の非交配雌と比較して同程度の差はなかった。

腎臓では、遠位尿細管あるいは集合管の空胞変性が 300/150 mg/kg 群の 3 例に認められた。

副腎では 300/150 mg/kg 群の 1 例に束状帯細胞に限局性の空胞化が認められた。

卵巣では、300/150 mg/kg 群の 5 例に異常は認められなかった。

全哺育児が死亡した 30 mg/kg 群の 1 例 (動物番号 F02017) では、剖検時に異常が認められた副腎に束状帯細胞の肥大がみられた他、胸腺の萎縮、前胃粘膜固有層の浮腫を伴う潰瘍、肝細胞の門脈周囲性の脂肪化と小肉芽腫が観察された。

⑥サテライト群の投与終了時剖検例 (Table 34-2, Appendix 34-2)

非交配雌の投与終了時剖検例、対照群 5 例および 300/150 mg/kg 群 3 例の病理組織所見は以下の通りである。

肺では、300/150 mg/kg 群の 1 例に肺胞内泡沫細胞の集簇が観察されたが、ごく軽度な変化であった。

肝臓では、核の大小不同を伴うびまん性の肝細胞の肥大が 300/150 mg/kg 群の 3 例に認められ、頻度および程度とも対照群と比較して有意に増加した。その他、肝細胞の門脈周囲性の脂肪化と小肉芽腫が

300/150 mg/kg 群で認められたが、対照群にもみられた軽度な変化であった。

胃では、前胃の粘膜固有層の浮腫を伴う扁平上皮の過形成が 300/150 mg/kg 群の 1 例に、また同群の別の 1 例に腺胃粘膜のびらんが観察された。

脾臓では、300/150 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、対照群と比較して程度の差はなかった。

腎臓では遠位尿細管あるいは集合管の空胞変性が 300/150 mg/kg 群の 3 例に観察され、頻度および程度とも対照群と比較して有意に増加した。

その他の器官に被験物質投与の影響を示唆する変化は認められなかった。

⑦サテライト群の回復観察例 (Table 34-3, Appendix 34-3)

回復 15 日に剖検した非交配雌、対照群の 5 例および 300/150 mg/kg 群の 3 例については、投与終了時の剖検例で被験物質の影響が示唆された肝臓、脾臓および腎臓について病理組織学検査を実施した。病理組織所見は、以下の通りである。

肝臓では、対照群にもみられた門脈周囲性の肝細胞の脂肪化が 300/150 mg/kg 群の 2 例で認められた。

脾臓では、対照群および 300/150 mg/kg 群の全例に髄外造血および褐色色素の沈着が観察されたが、投与終了時と比較して程度の差はなかった。

腎臓では、皮質の好塩基性尿細管と乳頭部の壊死が 300/150 mg/kg 群の 1 例に観察されたが、ごく軽度な変化であった。その他、対照群にもみられた髄質の鉍質沈着が 300/150 mg/kg 群の 1 例に観察された。

2. 生殖能力

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

投与開始後に異常性周期を示した動物が 30 mg/kg 群で 1 例、300/150 mg/kg 群で 2 例認められたが、交尾は全例で確認された。同居開始日から交尾確認日までの日数は、300/150 mg/kg 群で対照群と比較して有意に短縮したが、投与期間中の平均発情回帰日数、同居開始日から交尾確認日までの間に回帰した発情期の回数に被験物質投与の影響を示唆する変化は認められなかった。しかし、100 および 300/150 mg/kg 群の交尾雌が全て不妊であったことから、100 および 300/150 mg/kg 群の妊娠率は 0%となった。なお、100 および 300/150 mg/kg 群の回復観察に供した各群 5 匹の雄動物と無処置雌を再交配させた結果、全例の交尾は確認されたが、交尾雌はいずれも不妊であった。

2) 出産率および妊娠期間 (Table 37, Appendix 37)

30 mg/kg 群の妊娠期間および出産率に被験物質投与の影響は認められなかった。

3) 分娩および哺育状態 (Table 37, Appendix 37)

30 mg/kg 群の 1 例(動物番号 F02017)で分娩状態の不良(食殺)が観察され、分娩日に生存児は観

察されなかったが、その他の動物の分娩状態および哺育状態に異常は認められなかった。

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

30 mg/kg 群の黄体数、着床数および着床率に被験物質投与の影響は認められなかった。

3. 出生児

1) 生存 (Table 37, Appendix 37)

30 mg/kg 群の全哺育児が死亡した 1 例以外では、産児数、出産生児数、分娩率、生児出産率、出生率、哺育 0 日および哺育 4 日の性比、新生児生存率に被験物質投与の影響を示唆する変化は認められなかった。また、哺育 0 日に産児の外表奇形は観察されなかった。

2) 体重 (Table 38, Appendix 38)

哺育 0 日では、30 mg/kg 群の雌の体重が対照群と比較して有意に低下した。哺育 4 日では、30 mg/kg 群と対照群の出生児体重に有意差は認められなかった。

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

死亡児および哺育 4 日の生存児の剖検では、外表奇形および内蔵異常は観察されなかった。

考察

雌雄ラットの交配前(2 週間)および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、雌では妊娠期間を通して周産期(哺育 4 日まで)に 4-isopropylbenzaldehyde を経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性

死亡あるいは瀕死動物が 300/150 mg/kg 群の交配雌 4 匹および非交配雌 4 匹にみられた。これらの例では、生存時に自発運動の低下、鎮静、排便量の減少、痩せなどが観察され、同群の生存雌や投与量設定のための予備試験においても同様の症状が観察されていることから、いずれも被験物質投与の影響と考えられる。本被験物質は、ユーカリやクミンなどの精油成分で鎮静作用¹⁾や麻痺作用を有するが、大量摂取によりそれらの作用が重篤化したものと推察された。

雄では被験物質の影響と考えられる一般状態の異常は観察されなかったが、自発運動測定において立ち上がり回数の減少が 300/150 mg/kg 群にみられ、体重増加抑制が 300/150 mg/kg 群で、摂餌量の低下が 100 mg/kg 以上の群で観察された。体重増加抑制は 300/150 mg/kg 群の非交配雌で、摂餌量の低下は 300/150 mg/kg 群の交配雌および非交配雌においても認められていることから、これらの変

化は被験物質投与の影響と考えられる。

300/150 mg/kg 群の非交配雌では、尿検査で尿量の増加、尿比重の低下、カリウムイオンおよび塩素イオン濃度の低下、血液生化学検査でカルシウム濃度の低下、さらには腎臓の相対重量の増加がみられ、腎臓の病理組織学検査では遠位尿細管あるいは集合管の空胞変性が観察された。同様の組織所見は、300/150 mg/kg 群の死亡した雌と不妊雌でも観察されていることから、これらの変化は被験物質投与による腎臓へ影響と考えられる。血液学検査では MCHC と血小板数の低下が 300/150 mg/kg 群の非交配雌、血小板数の低下傾向が 100 mg/kg 以上の群の不妊雌でみられたことから、これらの変化も腎機能の低下に関連したものと推察される。

300/150 mg/kg 群の雄においても、血中の尿素窒素濃度と無機リン濃度の増加、カルシウム濃度の低下、腎臓の相対重量の増加など腎臓への影響を示唆する変化はみられたが、腎臓の病理組織学検査で影響を示唆する所見は観察されなかった。

肝臓の重量増加が 100 mg/kg 以上の群の雄と 300/150 mg/kg 群の非交配雌、100 および 300/150 mg/kg 群の不妊雌、さらには 30 mg/kg 群の分娩雌で認められ、病理組織学検査では核の大小不同を伴うびまん性肝細胞肥大が 100 mg/kg 以上の群の雄、300/150 mg/kg 群の非交配雌、100 および 300/150 mg/kg 群の不妊雌で観察されたことから、これらは薬物代謝酵素の誘導に伴う変化が疑われた。しかしながら、肝細胞の空胞変性が 300/150 mg/kg 群の死亡した雌にみられ、小肉芽腫の増加と単細胞壊死が 100 mg/kg 以上の群の雄および 300/150 mg/kg 群の不妊雌に、血液生化学検査においては総蛋白と総コレステロール濃度の低下と AST の増加が 300/150 mg/kg 群の雄で、アルブミン濃度の低下が 300/150 mg/kg 群の非交配雌と 100 および 300/150 mg/kg 群の不妊雌で認められたことから肝臓への毒性影響と判断した。

30 mg/kg 群の分娩雌では、血液生化学検査でグルコース濃度の増加がみられた。雄および非交配雌に同様の変化は認められていないが、5 例中 3 例で背景データの範囲を上回る値を示したことから被験物質の影響が疑われたが、その機序は不明であった。

投与終了時の雄では、300/150 mg/kg 群に精巣の相対重量が低下し、病理組織学検査では精細管の萎縮、伸長精子細胞の減少、ライディッヒ細胞の過形成などが両側性にみられたことから、精巣への毒性影響と判断された。一方、100 mg/kg 群では精巣上体の相対重量が増加し、管腔内精子数の減少と細胞残屑の増加が 100 mg/kg 以上の群で観察されたことから、被験物質の影響が示唆された。雌では、卵巢重量の低下傾向が 100 mg/kg 以上の群の不妊雌で認められ、卵巢への影響を示唆する変化はみられたが、卵巢の病理組織学検査で異常は観察されなかった。

30 mg/kg 以上の群の雄でみられた胸腺の重量低下については、原因は不明だが、死亡した雌において腸間膜リンパ節、脾臓の赤脾髄および白脾髄、さらには胸腺の萎縮が観察されていることなどから、被験物質投与によりリンパ球系細胞の増殖が抑制された可能性が考えられた。

2. 毒性の回復性

被験物質投与によると考えられる体重増加の抑制が 100 mg/kg 以上の群の雄および 300/150 mg/kg

群の非交配雌にみられ、血液生化学検査では総蛋白濃度の低下が 300/150 mg/kg 群の非交配雌にみられた。しかし、回復期間中の一般状態観察、摂餌量、尿検査および血液学検査においては、被験物質の影響はみられなかった。肝臓重量の増加は、回復終了時には消失したが、病理組織学検査では核の大小不同を伴うびまん性の肝細胞肥大が 100 mg/kg 以上の群の雄で認められた。胸腺の重量低下は、回復終了時の雄では消失したが、胸腺重量の増加が非交配雌でみられた。

被験物質投与によると考えられる精巣および精巣上体の重量低下が 300/150 mg/kg 群にみられ、300/150 mg/kg 群の精巣では精細管の萎縮、伸長精子細胞の減少、ライディッヒ細胞の過形成および多核巨細胞が、100 mg/kg 以上の群の精巣上体では、管腔内精子数の減少および管腔内細胞残屑が観察され、回復性は確認できなかった。

3. 生殖発生毒性

100 および 300/150 mg/kg 群の交尾雌は全て不妊であり、100 および 300/150 mg/kg 群の雄動物と再交配させた無処置雌も全例が不妊であったことから、100 mg/kg 以上の量は、雄動物の妊孕性を著しく低下させることが判明した。前述の通り、300/150 mg/kg 群の雄では両側性に精巣の萎縮が確認されており、100 mg/kg 群においても精巣上体に異常が認められていることから、本被験物質は雄性生殖器に悪影響を及ぼすと考えられる。しかしながら、精巣上体を除く副生殖腺には明らかな異常がみられず、全例で交尾が確認されたことから、交尾能力には影響を及ぼさないものと推察された。本被験物質と同じ芳香族アルデヒド類の 4-メトキシベンズアルデヒドについても、ラットを用いる反復経口投与毒性・生殖発生毒性併合試験で雄の妊孕性の低下が報告されている²⁾。

100 mg/kg 以上の群の雌の受胎能については確認することができなかったが、性周期および 300/150 mg/kg 群の卵巣の病理組織学検査では、被験物質の影響を示唆する変化は観察されなかった。

30 mg/kg 群の妊娠期間および出産率に被験物質投与の影響は認められず、分娩状態、哺育状態、黄体数、着床数および着床率に被験物質投与の影響は認められなかったことから、30 mg/kg の用量は母動物に影響を及ぼさないと考えられる。また、30 mg/kg 群の出生児についても、生存性および形態に被験物質投与の影響は認められなかったが、哺育 0 日の雌児の体重が 30 mg/kg 群で低下した。30 mg/kg 群では哺育 4 日の母動物の体重も減少していることから、被験物質投与の影響は否定できなかった。なお、ラットを用いる反復経口投与毒性・生殖発生毒性併合試験において、4-メトキシベンズアルデヒド²⁾では出生児の体重低下は認められていないが、2-ヒドロキシベンズアルデヒド³⁾では出生児体重の低下傾向が 160 mg/kg 群で認められている。

死亡児および哺育 4 日の生存児の剖検では、外表奇形および内臓異常は観察されなかったことから、出生児の形態への影響はないものと考えられる。

4. 無毒性量

胸腺の重量低下が 30 mg/kg 群の雄で、肝臓の重量増加と血中グルコース濃度の増加が 30 mg/kg

群の分娩雌で観察されたことから、雌雄動物の反復投与毒性に対する無毒性量 (NOAEL) は 30 mg/kg/day 未満と判断された。また、30 mg/kg 群では、分娩雌の哺育 4 日の体重が減少し、哺育 0 日の雌児の体重が低下したことから生殖発生毒性に対する無毒性量も 30 mg/kg/day 未満と判断された。

参考文献

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- 3) [REDACTED] 2-ヒドロキシベンズアルデヒドのラットを用いる反復経口投与毒性・生殖発生毒性併合試験. 化学物質毒性試験報告 4: 153-164 (1996)

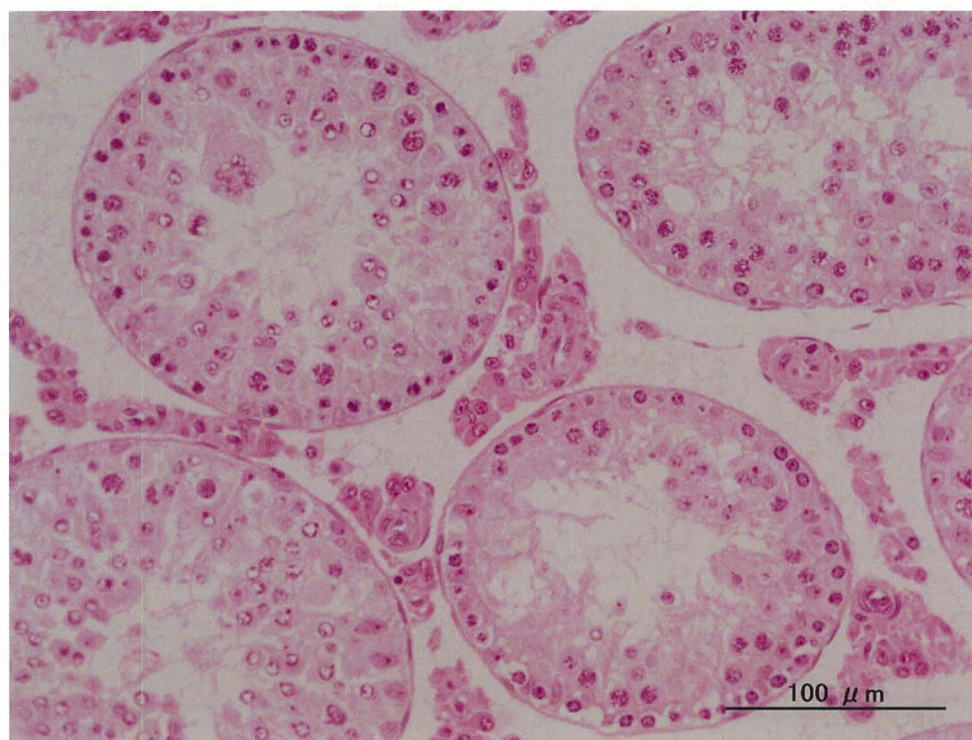


Photo 1 Atrophy of the seminiferous tubules, and the multinucleated giant cells in the seminiferous tubule were observed in the 300/150 mg/kg group.

Annex A

検査成績書 036-08545

<https://www.siyaku.com/cgi-bin/gx.cgi/AppLogic+ufg...>

検 査 成 績 書

財団法人食品薬品安全センター 秦野研究所/化学物質管理室 御
中2012年7月3日
和光純薬工業株式会
社

Code No. 036-08545

p-イソプロピルベンズアルデヒド(クミンアルデヒド)

規格/等級

Lot No. KWE2088

数量 500g

検査項目	検査成績	規格値
外観	無色、澄明の液体	無色～わずかにうすい黄色、澄明の液体
密度(20℃)	0.978g/ml	0.977～0.983g/ml
屈折率 $n_{20/D}$	1.532	1.527～1.533
含量(毛管カラムGC)	99.6%	95.0%以上
検査年月日	2009/12/22	

判定	合格	検査責任者	
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成績書発行番号 9861459

Annex B

SOP/CHE/001
採用開始 2010年4月23日

安定性試験結果

試験番号	R - 12 - 002
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被験物質：4-isopropylbenzaldehyde
ロット番号：KWE2088
媒体：トウモロコシ油

調製年月日 2012年9月11日
測定年月日 A 2012年9月11日(調製直後)
B 2012年9月19日(調製後8日)
保管条件 室温、遮光

調製濃度 (mg/mL)	A				B				
	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	試料 番号	測定濃度 (mg/mL)	含量 ^{a)} (%)	ばらつき ^{b)} (%)	残存率 ^{c)} (%)
7.50	1	7.716	102.9	101.1	7	7.638	101.8	100.4	100.0
	2	7.592	101.2	99.4	8	7.618	101.6	100.2	99.8
	3	7.598	101.3	99.5	9	7.557	100.8	99.4	99.0
	平均	7.635	101.8		平均	7.604	101.4		99.6
75.0	4	76.19	101.6	100.1	10	76.15	101.5	99.9	100.0
	5	75.90	101.2	99.7	11	75.84	101.1	99.5	99.6
	6	76.29	101.7	100.2	12	76.73	102.3	100.6	100.8
	平均	76.12	101.5		平均	76.24	101.6		100.1

a): 各測定時の測定濃度/調製濃度×100 b): 各測定時の測定濃度/各測定時の平均測定濃度×100 c): 各測定時の測定濃度/初回の平均測定濃度×100

安定性の判断基準(溶液検体)

各試料採取時点(調製直後および各保管期間後)の平均含量がそれぞれ調製濃度の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%以内であり、かつ、初回(調製直後)の測定平均値に対する各保管期間後の測定値の比(残存率)の平均値が90.0%以上を示す期間を投与検体の有効期間とする。

Annex C

1. 被験物質原体の安定性の測定方法

- ① 使用機器
フーリエ変換赤外分光光度計 (FTIR-8300) 島津製作所
- ② 測定条件
測定方法 液膜法
波数範囲 4000～400 cm^{-1}
- ③ 測定方法
被験物質1、2滴を2枚の窓板(臭化カリウム)の間に挟み、測定する。対照は、測定雰囲気バックグラウンド吸収とする。

2. 投与検体中の被験物質含量測定法

- ① 試薬
蒸留水 (HPLC用) 和光純薬工業 アセトニトリル (HPLC用) 和光純薬工業
メタノール (HPLC用) 和光純薬工業 2-プロパノール (HPLC用) 和光純薬工業
- ② 試液の調製(代表例)
移動相及びオートインジェクタ洗浄液
蒸留水及びアセトニトリルを6:4 (v/v)の割合で混合する。
- ③ 使用機器
電子天秤 (R200D) ザルトリウス
高速液体クロマトグラフ (HPLC) システム 島津製作所
主要構成: LC-10AS (ポンプ)、SIL-10A (オートインジェクタ)、CTO-10AS VP (カラムオーブン)、SPD-10A (検出器)、SCL-10A VP (システムコントローラ)、C-R7AまたはC-R7A plus (データ処理装置)
- ④ 標準溶液の調製
被験物質約50 mgを精密に量り、メタノールに溶解して正確に25 mLとする。この液1 mLを正確にとり、メタノールを加えて正確に10 mLとし、さらにこの液1 mLを正確にとり、メタノールを加えて正確に20 mLとして、標準原液(約10 $\mu\text{g}/\text{mL}$)とする。この標準原液1、1および2 mLを正確にとり、メタノールを加えてそれぞれ正確に20、10および10 mLとし、標準溶液(約0.5、1および2 $\mu\text{g}/\text{mL}$ 、各濃度 $n=1$)を調製する。
- ⑤ 試料溶液の調製
被験物質調製液の1 mLを正確にとり、2-プロパノールで少なくとも50倍以上希釈し、以降、メタノールで適宜希釈して試料溶液(約1 $\mu\text{g}/\text{mL}$)を調製する。試料溶液は、被験物質調製液の採取から $n=3$ で調製する。
- ⑥ 検量線の作成および被験物質調製液中被験物質濃度の算出
試料溶液および標準溶液を高速液体クロマトグラフィーにより測定する。標準溶液は $n=3$ で測定し、得られた4-IBAのピーク面積と調製濃度を基に、最小二乗法により検量線を作成する。試料溶液は、各 $n=1$ で測定し、得られた4-IBAのピーク面積から、先の検量線を用いて、試料溶液中の4-IBAの濃度を求める。さらに、希釈係数を乗じて被験物質調製液中の4-IBA濃度を算出し、調製濃度に対する割合(含量、%)および各測定濃度の平均値に対するばらつき(%)を算出する。
- ⑦ HPLC 測定条件
検出器 紫外分光光度計(測定波長255 nm)
分析カラム XTerra RP18 (内径3.0 mm、長さ100 mm、粒子径3.5 μm 、Waters)
移動相 蒸留水/アセトニトリル混液(6:4 v/v)
流量 0.8 mL/min
カラム設定温度 40°C
試料設定温度 室温
試料注入量 10 μL
オートインジェクタ洗浄液 蒸留水/アセトニトリル混液(6:4 v/v)
システムの適合性 SOP/CHE/001に従い、測定開始前および測定終了後に、標準溶液(約1 $\mu\text{g}/\text{mL}$)を1回ずつ測定し、ピーク保持時間の変動が $\pm 3.0\%$ 以内、ピーク強度の変動が $\pm 5.0\%$ 以内であることを確認する。
- ⑧ 数値の取り扱い
SOP/CHE/001に従い、調製濃度は有効数字4桁目を四捨五入して有効数字3桁で、測定濃度および平均測定濃度は有効数字5桁目を切り捨てて有効数字4桁で表示し、含量、平均含量およびばらつきは小数点以下第2位を四捨五入して少数点以下第1位まで表示する。

Annex D-1

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R - 12 - 002
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含 量 試 験 結 果

被験物質：4-isopropylbenzaldehyde
ロット番号：KWE2088
媒 体：トウモロコシ油

調製年月日：2012年9月24日
測定年月日：2012年9月24日

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 $B/A \times 100$ (%)	平均含量 (%)	ばらつき $B/C \times 100$ (%)
13	7.50	7.610	7.549	101.5	100.7	100.8
14		7.541		100.5		99.9
15		7.497		100.0		99.3
16	25.0	25.40	25.29	101.6	101.2	100.4
17		25.74		103.0		101.8
18		24.73		98.9		97.8
19	75.0	76.37	75.73	101.8	101.0	100.8
20		76.00		101.3		100.4
21		74.82		99.8		98.8

含量の判断基準(溶液検体)

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

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R - 12 - 002
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含 量 試 験 結 果

被験物質：4-isopropylbenzaldehyde

調製年月日：2012年10月13日

ロット番号：KWE2088

測定年月日：2012年10月15日

媒 体：トウモロコシ油

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 $B/A \times 100$ (%)	平均含量 (%)	ばらつき $B/C \times 100$ (%)
22	37.5	38.22	38.53	101.9	102.7	99.2
23		39.01		104.0		101.2
24		38.36		102.3		99.6

含量の判断基準(溶液検体)

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 1-1. General conditions of male rats

Group	Number of males and general conditions	Days of administration																																																								
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25								
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	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	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12						
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12				
4-IBA 30 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12			
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
4-IBA 100 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
4-IBA 300/150 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of males and general conditions	Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Control (vehicle: corn oil)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	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		
	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		
4-IBA 30 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	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	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
4-IBA 100 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	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		
	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		
4-IBA 300/150 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7		
	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		
	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		

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of males and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: corn oil)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4-IBA 100 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4-IBA 300/150 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

[illegible]

Pre: Before administration. Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of females and general conditions	Days of administration																																		
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre		
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	5	
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
	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	
4-IBA 300/150 mg/kg	Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3		
	General appearance, No abnormality	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	5	3		
	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	1	1	1	1	1	1	1	0		

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of females and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: corn oil)	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4-IBA 300/150 mg/kg	Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	General appearance, No abnormality	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 3. General conditions in dams during pregnancy

[illegible]

Pre: Before administration. Post: after administration

General conditions in non-pregnant females after successful mating

[illegible]

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation											
		0		1		2		3		4		5	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: corn oil)	Number of dams	9	9	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	9	9	11	11	11	11	11	11	11	11	11	11
4-IBA 30 mg/kg	Number of dams	7	6	9	9	9	9	9	9	9	9	9	9
	General appearance, No abnormality	7	6	9	9	9	9	9	9	9	9	9	9

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery ^a	
				8	15	24	30	36	42	7	14
[Urination] (frequency/30sec)	Control (vehicle: control)	12	3 ^b	1	1	1	2	1	0	0	0
	4-IBA (30 mg/kg)	12	3	2	1	2	2	3	2		
	4-IBA (100 mg/kg)	12	1	0	1	0	2	1	0	3	1
	4-IBA (300/150 mg/kg)	12	0	2	1	2	1	2	0	2	1
[Defecation] (frequency/30sec)	Control (vehicle: control)	12	5 ^b	1	1	3	2	0	1	0	0
	4-IBA (30 mg/kg)	12	2	3	2	2	0	3	2		
	4-IBA (100 mg/kg)	12	2	0	1	1	1	0	1	0	2
	4-IBA (300/150 mg/kg)	12	1	0	0	1	0	0	0	0	0

^a The recovery test was performed in 5 animals for each of the 0 and 300/150 mg/kg groups.

^b Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment					The lactation period
				8	15	24	30	36	
[Straub tail]	Control (vehicle: corn oil)	12	0 ^a	0	0	0	0	0	0
Tail elevation	4-IBA (30 mg/kg)	12	0	0	0	0	1	0	0 (11)
	4-IBA (100 mg/kg)	12	0	0	0	0	0	0	0 (12)
	4-IBA (300/150 mg/kg)	12	0	0	0 (11)	0 (10)	0 (10)	0 (8)	0 (8)
[Urination]	Control (vehicle: corn oil)	12	1 ^b	0	0	0	0	0	0
(frequency/30sec)	4-IBA (30 mg/kg)	12	0	1	0	0	0	0	1 (11)
	4-IBA (100 mg/kg)	12	2	3	1	1	0	1	0 (12)
	4-IBA (300/150 mg/kg)	12	0	0	0 (11)	0 (10)	0 (10)	0 (8)	1 (8)
[Defecation]	Control (vehicle: corn oil)	12	0 ^b	0	0	0	0	0	0
(frequency/30sec)	4-IBA (30 mg/kg)	12	0	0	0	0	0	0	0 (11)
	4-IBA (100 mg/kg)	12	0	0	0	0	0	1	0 (12)
	4-IBA (300/150 mg/kg)	12	0	0	0 (11)	0 (10)	2 (10)	0 (8)	0 (8)

^a Values represent number of animals with the findings.

^b Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment						Days of recovery	
				8	15	24	30	36	42	7	14
[Straub tail] Tail elevation	Control (vehicle: com oil)	10	0 ^a	0	0	0	0	0	0	0 (5)	0 (5)
	4-IBA (300/150 mg/kg)	10	0	0 (9)	0 (9)	0 (6)	0 (6)	0 (6)	0 (6)	0 (3)	0 (3)
[Urination] (frequency/30sec)	Control (vehicle: com oil)	10	1 ^b	0	1	0	0	0	1	0 (5)	0 (5)
	4-IBA (300/150 mg/kg)	10	0	0 (9)	1 (9)	0 (6)	0 (6)	1 (6)	0 (6)	0 (9)	0 (9)
[Defecation] (frequency/30sec)	Control (vehicle: com oil)	10	0 ^b	0	0	0	0	0	0	0 (5)	0 (5)
	4-IBA (300/150 mg/kg)	10	0	0 (9)	0 (9)	0 (6)	0 (6)	0 (6)	0 (6)	0 (3)	0 (3)

^a Values represent number of animals with the findings.

^b Values represent total score of each group.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 7-1. Body weights of male rats

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of males	12	12	12	12
Days of administration				
1	381.0 ± 17.6	380.5 ± 16.3	379.3 ± 16.9	378.7 ± 16.1
4	393.2 ± 18.8	390.9 ± 19.1	386.1 ± 21.7	374.8 ± 17.5
7	405.8 ± 20.0	401.6 ± 23.1	397.6 ± 26.6	385.2 ± 15.9
14	430.5 ± 23.0	423.9 ± 27.9	420.0 ± 34.7	398.7 ± 17.4 *
21	448.9 ± 24.8	443.2 ± 30.6	437.8 ± 34.6	413.9 ± 19.1 **
28	472.1 ± 27.9	464.9 ± 34.2	454.9 ± 36.8	439.7 ± 24.5
35	494.9 ± 32.1	478.9 ± 33.9	473.6 ± 37.5	455.6 ± 26.9 *
42	512.5 ± 34.6	494.0 ± 33.9	485.6 ± 36.7	466.5 ± 28.8 **

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of males	5	5	5
Days of recovery			
1	534.6 ± 30.9	467.2 ± 31.4 **	452.1 ± 29.4 **
7	546.6 ± 34.5	480.7 ± 36.3 *	473.8 ± 27.7 **
14	552.8 ± 39.6	490.7 ± 36.2 *	489.7 ± 29.6 *

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 8-1. Body weights of female rats

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	245.7 ± 14.7	244.0 ± 11.4	246.3 ± 14.4	242.4 ± 14.3
4	249.9 ± 15.1	247.0 ± 13.5	248.3 ± 13.3	234.2 ± 22.0
7	253.6 ± 16.1	250.3 ± 12.8	251.8 ± 15.0	243.6 ± 19.1
14	263.7 ± 16.8	260.9 ± 15.4	260.7 ± 14.0	255.6 ± 24.2 (11)

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	4-IBA 300/150 mg/kg	
Number of females	10	10	
Days of administration			
1	252.0 ± 15.0	245.5 ± 13.9	
4	257.2 ± 12.9	235.9 ± 17.9 **	
7	263.1 ± 15.8	233.6 ± 30.7 *	
14	276.9 ± 19.7	252.7 ± 18.1 * (9)	
21	293.1 ± 23.4	261.0 ± 36.6 * (7)	
28	300.2 ± 23.6	277.5 ± 20.7 (6)	
35	306.5 ± 23.3	281.4 ± 23.8 (6)	
42	312.0 ± 26.3	280.3 ± 37.5 (6)	

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 300/150 mg/kg
Number of females		5	3
Days of recovery			
	1	318.8 ± 21.6	259.2 ± 42.7 *
	7	324.4 ± 19.7	277.8 ± 23.6 *
	14	326.0 ± 29.8	283.2 ± 36.5

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams	11	10
Days of pregnancy		
0	276.7 ± 18.8	266.2 ± 19.4
7	311.4 ± 23.1	300.4 ± 22.9
14	349.4 ± 29.1	334.7 ± 20.7
20	428.6 ± 33.6	414.2 ± 31.0

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 10. Body weights of dams during lactation

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams	11	10
Days of lactation		
0	325.9 ± 39.7	322.3 ± 24.1
4	341.3 ± 27.1	317.3 ± 31.5 (9)

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of males	12	12	12	12
Days of administration				
1	26.5 ± 2.3	25.1 ± 2.4	22.6 ± 2.4 *	19.8 ± 5.3 **
7	25.2 ± 2.7	23.3 ± 2.6	23.5 ± 2.8	26.0 ± 3.3
14	21.7 ± 3.0	21.4 ± 2.2	21.3 ± 2.0	23.1 ± 6.1
29	24.2 ± 3.1	22.9 ± 2.0	23.5 ± 1.6	24.2 ± 3.2
35	23.3 ± 2.8	21.5 ± 2.1	21.7 ± 1.9	21.7 ± 2.4
41	24.8 ± 2.8	22.8 ± 2.3	24.1 ± 2.5	24.3 ± 3.6

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of males		5	5	5
Days of recovery	6	29.0 ± 3.0	27.4 ± 4.0	25.2 ± 1.0
	12	29.5 ± 2.7	27.9 ± 4.3	28.3 ± 1.4

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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of females	12	12	12	12
Days of administration				
1	17.1 ± 2.9	17.2 ± 2.0	14.8 ± 3.0	13.1 ± 2.3 **
7	19.2 ± 2.4	17.9 ± 2.8	19.3 ± 3.0	19.9 ± 4.4
14	14.3 ± 3.4	13.7 ± 2.4	15.1 ± 2.7	15.6 ± 6.1 (11)

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 300/150 mg/kg	
Number of females		10		10	
Days of administration					
	1	16.1	± 2.6	12.3	± 1.7 **
	7	20.1	± 2.3	17.9	± 7.2 (9)
	14	16.8	± 2.4	15.4	± 8.2 (9)
	21	18.4	± 3.9	17.0	± 7.6 (7)
	29	17.4	± 3.5	18.2	± 4.1 (6)
	35	16.9	± 2.9	17.4	± 1.9 (6)
	41	17.0	± 2.3	17.5	± 4.1 (6)

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 300/150 mg/kg
Number of females		5	3
Days of recovery			
	6	20.6 ± 2.7	21.0 ± 2.0
	12	19.9 ± 3.3	22.1 ± 6.3

Each value shows mean (g) ± S.D.

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

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group		Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams		11	10
Days of pregnancy			
	0	21.0 ± 3.3	19.6 ± 3.8
	7	23.4 ± 4.2	21.8 ± 3.2
	14	24.6 ± 4.2	22.4 ± 2.4
	20	17.5 ± 5.2	15.4 ± 7.7

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams	11	9
Days of lactation		
3	35.0 ± 6.0	30.5 ± 5.5

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 15. Functional findings of male rats at the last week of the dosing period

Group	Control (vehicle: corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
<u>Male</u>				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 16. Functional findings of female rats at the last week of the dosing period

Group	Control (vehicle: corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
<u>Female, dam</u>				
Number of animals	5	5		
Righting reflex	100	100		
Visual placing	100	100		
Pupillary reflex	100	100		
Startle reaction	100	100		
Preyer's reaction	100	100		
Withdrawal reflex	100	100		
Eyelid reflex	100	100		
<u>Female, satellite group</u>				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 17. Assessment of grip strength of male rats at the last week of the dosing period

Group	Control (vehicle: corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA(300/150 mg/kg)
Number of males	5	5	5	5
Forelimb	0.949 ± 0.146	0.863 ± 0.161	0.941 ± 0.105	1.004 ± 0.147
Hindlimb	0.525 ± 0.200	0.545 ± 0.113	0.484 ± 0.113	0.564 ± 0.094

Each value shows mean (kg) ±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 18. Assessment of grip strength of female rats at the last week of the dosing period

Group	Control (vehicle :corn oil)	4-IBA (30 mg/kg)
Number of females	5	5
Forelimb	0.975 ± 0.152	0.975 ± 0.149
Hindlimb	0.572 ± 0.118	0.571 ± 0.064

Each value shows mean (kg) ±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 19. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

Group	Control (vehicle :corn oil)	4-IBA (300/150 mg/kg)
Number of females	5	5
Forelimb	0.930 ± 0.184	0.967 ± 0.117
Hindlimb	0.558 ± 0.089	0.591 ± 0.099

Each value shows mean (kg) ±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 20-1 . Motor activity of male rats at the last week of the dosing period

Group	Control (vehicle: corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
Number of males	5	5	5	5
Ambulation (counts)				
5min	1084 ± 120	1020 ± 182	1255 ± 350	1008 ± 269
10min	814 ± 258	958 ± 81	1112 ± 315	860 ± 212
15min	721 ± 263	589 ± 169	923 ± 333	344 ± 172
20min	508 ± 357	495 ± 171	701 ± 523	467 ± 365
Total	3127 ± 945	3062 ± 381	3991 ± 1455	2680 ± 732
Rearing (counts)				
5min	33 ± 6	28 ± 8	32 ± 6	32 ± 11
10min	20 ± 8	28 ± 5	26 ± 6	19 ± 11
15min	20 ± 7	15 ± 9	17 ± 3	5 ± 5 **
20min	6 ± 5	11 ± 7	15 ± 14	10 ± 9
Total	78 ± 20	83 ± 15	91 ± 18	67 ± 28

Each value shows mean±S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 20-2. Motor activity of male rats at the last week of the recovery period

Group	Control (vehicle: corn oil)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
Number of males	5	5	5
Ambulation (counts)			
5min	1242 ± 120	1194 ± 102	1320 ± 205
10min	1113 ± 101	1098 ± 96	1175 ± 363
15min	1040 ± 139	959 ± 214	1011 ± 459
20min	927 ± 185	803 ± 122	1005 ± 459
Total	4322 ± 445	4054 ± 502	4511 ± 1446
Rearing (counts)			
5min	39 ± 11	41 ± 10	29 ± 9
10min	35 ± 6	31 ± 8	22 ± 9
15min	29 ± 10	25 ± 8	22 ± 14
20min	21 ± 10	20 ± 4	13 ± 5
Total	125 ± 28	116 ± 21	87 ± 25

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 21. Motor activity of female rats at the last week of the dosing period

Group	Control (vehicle: corn oil)		4-IBA (30 mg/kg)	
Number of females	5		5	
Ambulation (counts)				
5min	1067	± 183	993	± 166
10min	651	± 194	586	± 155
15min	452	± 222	426	± 241
20min	281	± 201	265	± 212
Total	2452	± 562	2270	± 666
Rearing (counts)				
5min	27	± 8	23	± 7
10min	14	± 10	15	± 20
15min	8	± 8	4	± 2
20min	5	± 6	1	± 1
Total	54	± 23	43	± 23

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 22. Motor activity of female rats at the last week of the dosing period, satellite group

Group	Control (vehicle: corn oil)		4-IBA (300/150 mg/kg)	
Number of females	5		5	
Ambulation (counts)				
5min	1335	± 295	1167	± 210
10min	1081	± 261	937	± 222
15min	1086	± 486	752	± 239
20min	837	± 358	452	± 320
Total	4338	± 1331	3309	± 842
Rearing (counts)				
5min	33	± 5	39	± 8
10min	17	± 9	25	± 8
15min	18	± 6	17	± 11
20min	11	± 5	10	± 9
Total	79	± 17	91	± 25

Each value shows mean±S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality ^{a)}																					
		Color		Turbidity		pH					Protein			Glucose	Ketone			Bilirubin	Occult blood		Urobilinogen		
		Light yellow	Yellow	-	+	6.5	7.0	7.5	8.0	8.5	±	+	2+	-	-	±	+	-	-	2+	±	+	2+
Control (vehicle: corn oil)	5	5	0	4	1	3	1	0	0	1	0	4	1	5	1	0	4	5	5	0	2	3	0
4-IBA (30 mg/kg)	5	4	1	4	1	4	1	0	0	0	0	3	2	5	0	0	5	5	5	0	2	2	1
4-IBA (100 mg/kg)	5	5	0	5	0	1	1	1	1	1	1	4	0	5	2	0	3	5	5	0	5	0	0
4-IBA (300/150 mg/kg)	5	5	0	5	0	3	1	1	0	0	2	3	0	5	0	4	1	5	4	1	5	0	0

Group	Number of males	Urinary sediments ^{a)}								Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)} (mEq/L)			Electrolyte, gross volume ^{b)} (mEq/24 hr)		
		Red blood cells		White blood cells	Casts	Crystals		Epithelial cells	Na			K	Cl	Na	K	Cl	
		-	+	-	-	-	±	+		-	(mL/24hr)						
Control (vehicle: corn oil)	5	5	0	5	5	2	2	1	5	21.8 ±22.0	1.056 ±0.024	100.1 ±52.4	187.3 ±67.6	118.9 ±54.8	1.41 ±0.35	2.89 ±0.74	1.69 ±0.28
4-IBA (30 mg/kg)	5	5	0	5	5	1	4	0	5	13.0 ±5.9	1.058 ±0.016	107.5 ±33.5	179.9 ±21.1	125.4 ±31.6	1.25 ±0.24	2.26 ±0.85	1.49 ±0.30
4-IBA (100 mg/kg)	5	5	0	5	5	1	4	0	5	22.7 ±8.1	1.047 ±0.013	101.4 ±30.8	162.3 ±40.7	106.7 ±29.3	2.11* ±0.23	3.43 ±0.40	2.23 ±0.19
4-IBA (300/150 mg/kg)	5	4	1	5	5	2	3	0	5	28.3 ±11.4	1.043 ±0.005	82.5 ±8.3	162.0 ±15.4	92.6 ±14.3	2.34 ±1.01	4.59 ±1.93	2.58 ±0.97

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

Turbidity, -: negative; +: slight

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

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

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

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of males	Quality ^{a)}																			
		Color	Turbidity		pH				Protein				Glucose	Ketone			Bilirubin	Occult blood		Urobilinogen	
		Light yellow	-	+	6.5	7.0	7.5	8.0	-	±	+	2+	-	-	±	+	-	-	2+	±	+
Control (vehicle: corn oil)	5	5	4	1	0	3	0	2	1	0	3	1	5	2	1	2	5	5	0	2	3
4-IBA (100 mg/kg)	5	5	5	0	2	2	1	0	0	1	4	0	5	1	3	1	5	4	1	4	1
4-IBA (300/150 mg/kg)	5	5	5	0	0	3	2	0	0	1	4	0	5	2	3	0	5	5	0	5	0

Group	Number of males	Urinary sediments ^{a)}										Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells		White blood cells		Casts	Crystals		Epithelial cells		(mEq/L)			(mEq/24 hr)					
		-	+	-	+	-	-	±	+	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	0	5	5	1	3	1	5	0	29.6 ±28.4	1.054 ±0.031	89.0 ±51.2	171.7 ±72.7	111.0 ±58.6	1.59 ±0.30	3.51 ±1.29	2.07 ±0.48	
4-IBA (100 mg/kg)	5	4	1	5	5	1	4	0	4	1	20.4 ±2.4	1.048 ±0.007	78.5 ±12.0	166.9 ±9.1	94.4 ±17.7	1.59 ±0.23	3.40 ±0.31	1.90 ±0.22	
4-IBA (300/150 mg/kg)	5	5	0	5	5	1	4	0	5	0	33.2 ±17.4	1.034 ±0.011	62.3 ±20.6	139.8 ±40.8	77.3 ±25.4	1.81 ±0.27	4.11 ±0.52	2.24 ±0.24	

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

Turbidity, -: negative; +: slight

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

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

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

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of females	Quality ^{a)}																	
		Color		Turbidity	pH			Protein			Glucose		Ketone		Bilirubin	Occult	blood	Urobilinogen	
		Light yellow	Yellow	-	6.0	6.5	7.0	-	±	+	-	-	±	+	-	-	-	±	+
Control (vehicle: corn oil)	5	4	1	5	1	4	0	0	3	2	5	1	2	2	5	5	3	2	
4-IBA (300/150 mg/kg)	5	5	0	5	2	2	1	1	4	0	5	2	3	0	5	5	5	0	

Group	Number of females	Urinary sediments ^{a)}						Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)			(mEq/24 hr)					
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	5	5	3	2	5	10.4 ±5.2	1.060 ±0.020	104.0 ±36.4	187.0 ±43.3	130.3 ±46.4	0.95 ±0.26	1.80 ±0.65	1.20 ±0.37
4-IBA (300/150 mg/kg)	5	5	5	5	5	0	5	19.6 * ±5.2	1.035 * ±0.005	67.3 ±19.2	129.6 * ±27.0	73.2 * ±23.1	1.29 ±0.40	2.54 ±0.75	1.41 ±0.45

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of females	Quality ^{a)}																		
		Color	Turbidity		pH				Protein				Glucose	Ketone		Bilirubin	Occult blood		Urobilinogen	
		Light yellow	-	+	6.5	7.0	7.5	8.0	-	±	+	2+	-	-	±	-	-	2+	±	+
Control (vehicle: corn oil)	5	5	5	0	2	1	1	1	2	1	2	0	5	3	2	5	5	0	3	2
4-IBA (300/150 mg/kg)	3	3	2	1	1	1	1	0	1	1	0	1	3	3	0	3	2	1	3	0

Group	Number of females	Urinary sediments ^{a)}							Urine volume ^{b)}	Specific gravity ^{b)}	Electrolyte, density ^{b)}			Electrolyte, gross volume ^{b)}		
		Red blood cells	White blood cells	Casts	Crystals	Epithelial cells	(mEq/L)				(mEq/24 hr)					
		-	2+	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: corn oil)	5	5	0	5	5	2	3	5	13.0 ±4.1	1.054 ±0.024	108.9 ±50.3	165.4 ±61.1	120.0 ±75.8	1.29 ±0.39	2.02 ±0.60	1.38 ±0.59
4-IBA (300/150 mg/kg)	3	2	1	3	3	2	1	3	23.5 ±12.3	1.036 ±0.007	74.2 ±10.8	138.1 ±8.7	75.5 ±10.0	1.65 ±0.67	3.20 ±1.54	1.81 ±0.98

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

Turbidity, -: negative; +: slight

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative; ±: 0.03 ≤ and < 0.06 mg/dL; +: 0.06 ≤ and < 0.20 mg/dL; 2+: 0.20 ≤ and < 1.00 mg/dL

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

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

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

a), values represent as number of animals

b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		4-IBA (30 mg/kg)		4-IBA (100 mg/kg)		4-IBA (300/150 mg/kg)	
Number of males	5		5		5		5	
RBC ($\times 10^4/\mu\text{L}$)	808	± 41	844	± 42	808	± 21	797	± 30
Hemoglobin (g/dL)	14.6	± 0.9	15.0	± 0.5	14.5	± 0.2	14.2	± 0.6
Hematocrit (%)	41.7	± 2.1	43.7	± 1.7	42.0	± 1.1	41.3	± 1.9
MCV (fL)	51.5	± 0.6	51.8	± 1.5	52.0	± 1.9	51.8	± 2.2
MCH (pg)	18.1	± 0.2	17.8	± 0.3	17.9	± 0.6	17.8	± 0.7
MCHC (g/dL)	35.1	± 0.4	34.4	± 0.4	34.6	± 0.6	34.4	± 0.3
Platelet ($\times 10^4/\mu\text{L}$)	104.2	± 10.9	98.8	± 7.0	101.9	± 7.3	92.6	± 16.5
PT (sec)	16.3	± 2.0	17.4	± 2.0	15.3	± 1.5	15.7	± 1.1
APTT (sec)	24.8	± 2.9	25.4	± 1.1	23.2	± 1.8	22.8	± 1.5
WBC ($\times 10^2/\mu\text{L}$)	101.1	± 33.5	90.3	± 18.2	88.1	± 26.2	80.6	± 15.3
Differential leukocyte count (%)								
Neutrophil	18.7	± 10.2	18.8	± 4.1	22.2	± 4.6	13.7	± 4.1
Eosinophil	1.5	± 0.7	1.3	± 0.2	1.0	± 0.4	1.0	± 0.4
Basophil	0.0	± 0.0	0.0	± 0.1	0.0	± 0.0	0.0	± 0.0
Monocyte	3.3	± 1.7	3.5	± 0.5	3.7	± 0.7	3.7	± 1.1
Lymphocyte	76.5	± 11.2	76.4	± 4.2	73.1	± 4.5	81.6	± 3.8
Reticulocyte count (%)	3.01	± 0.54	3.09	± 0.75	3.13	± 0.85	3.25	± 0.42

Each value shows mean $\pm$ S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
Number of males	5	5	5
RBC ($\times 10^4/\mu\text{L}$)	856 $\pm$ 61	816 $\pm$ 39	849 $\pm$ 52
Hemoglobin (g/dL)	15.3 $\pm$ 0.7	14.5 $\pm$ 0.8	15.2 $\pm$ 1.0
Hematocrit (%)	43.2 $\pm$ 1.3	41.5 $\pm$ 2.2	43.8 $\pm$ 3.1
MCV (fL)	50.5 $\pm$ 2.5	50.9 $\pm$ 1.6	51.6 $\pm$ 1.8
MCH (pg)	17.9 $\pm$ 0.8	17.8 $\pm$ 0.5	17.9 $\pm$ 0.6
MCHC (g/dL)	35.5 $\pm$ 0.5	35.0 $\pm$ 0.4	34.6 $\pm$ 0.7
Platelet ($\times 10^4/\mu\text{L}$)	118.1 $\pm$ 5.6	112.5 $\pm$ 10.3	119.7 $\pm$ 11.1
PT (sec)	19.6 $\pm$ 3.6	18.0 $\pm$ 3.0	19.1 $\pm$ 1.3
APTT (sec)	29.8 $\pm$ 1.8	25.4 $\pm$ 1.5 **	29.4 $\pm$ 2.0
WBC ($\times 10^2/\mu\text{L}$)	64.1 $\pm$ 18.5	48.6 $\pm$ 11.0	55.9 $\pm$ 10.0
Differential leukocyte count (%)			
Neutrophil	20.8 $\pm$ 5.9	30.9 $\pm$ 8.6	22.2 $\pm$ 3.7
Eosinophil	2.1 $\pm$ 0.9	1.5 $\pm$ 0.5	1.5 $\pm$ 0.3
Basophil	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Monocyte	3.7 $\pm$ 1.4	3.0 $\pm$ 0.4	2.7 $\pm$ 0.4
Lymphocyte	73.3 $\pm$ 7.9	64.5 $\pm$ 9.0	73.6 $\pm$ 4.0
Reticulocyte count (%)	3.72 $\pm$ 0.36	3.94 $\pm$ 0.80	4.20 $\pm$ 0.62

Each value shows mean $\pm$ S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		4-IBA (30 mg/kg)	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	681	± 44	678	± 43
Hemoglobin (g/dL)	13.0	± 0.6	13.0	± 0.6
Hematocrit (%)	39.0	± 1.8	39.1	± 1.5
MCV (fL)	57.3	± 1.7	57.7	± 3.0
MCH (pg)	19.1	± 0.4	19.2	± 0.6
MCHC (g/dL)	33.3	± 0.8	33.3	± 0.9
Platelet ($\times 10^4/\mu\text{L}$)	119.5	± 17.1	125.2	± 18.8
PT (sec)	12.7	± 0.3	12.9	± 0.3
APTT (sec)	20.7	± 1.3	19.5	± 1.2
WBC ($\times 10^2/\mu\text{L}$)	101.8	± 18.1	113.9	± 4.4
Differential leukocyte count (%)				
Neutrophil	23.5	± 7.2	36.4	± 4.6 **
Eosinophil	0.6	± 0.2	0.4	± 0.3
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	3.6	± 1.4	3.6	± 0.5
Lymphocyte	72.4	± 6.2	59.6	± 4.5 **
Reticulocyte count (%)	8.45	± 4.31	6.39	± 2.80

Each value shows mean $\pm$ S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 26-1-2. Hematological findings of female rats at the end of the dosing period, non-pregnant females

Group	4-IBA (100 mg/kg)		4-IBA (300/150 mg/kg)	
Number of females	5		5	
RBC ($\times 10^4/\mu\text{L}$)	752	± 22	731	± 51
Hemoglobin (g/dL)	14.1	± 0.3	13.9	± 0.8
Hematocrit (%)	40.7	± 1.3	40.4	± 2.0
MCV (fL)	54.1	± 1.1	55.4	± 3.7
MCH (pg)	18.7	± 0.4	19.0	± 1.2
MCHC (g/dL)	34.6	± 0.5	34.3	± 0.6
Platelet ($\times 10^4/\mu\text{L}$)	91.5	± 3.6	87.7	± 4.7
PT (sec)	12.3	± 0.6	12.7	± 1.8
APTT (sec)	20.7	± 2.2	19.5	± 1.5
WBC ($\times 10^2/\mu\text{L}$)	72.4	± 25.1	75.7	± 18.0
Differential leukocyte count (%)				
Neutrophil	12.4	± 4.1	11.8	± 4.1
Eosinophil	1.2	± 0.1	0.7	± 0.4
Basophil	0.0	± 0.0	0.1	± 0.1
Monocyte	3.6	± 1.0	3.4	± 1.3
Lymphocyte	82.8	± 5.0	83.9	± 4.0
Reticulocyte count (%)	2.88	± 1.27	2.99	± 1.11

Each value shows mean $\pm$ S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		4-IBA (300/150 mg/kg)	
Number of females	5		3	
RBC ($\times 10^4/\mu\text{L}$)	763	± 57	750	± 18
Hemoglobin (g/dL)	14.2	± 0.6	14.1	± 0.3
Hematocrit (%)	40.0	± 1.4	41.0	± 1.5
MCV (fL)	52.6	± 3.6	54.7	± 0.8
MCH (pg)	18.7	± 1.2	18.8	± 0.1
MCHC (g/dL)	35.6	± 0.4	34.5	± 0.6 *
Platelet ($\times 10^4/\mu\text{L}$)	113.9	± 10.2	86.2	± 19.1 *
PT (sec)	12.3	± 0.5	13.4	± 1.1
APTT (sec)	20.0	± 0.5	19.0	± 2.1
WBC ($\times 10^2/\mu\text{L}$)	80.1	± 28.2	108.3	± 56.1
Differential leukocyte count (%)				
Neutrophil	8.7	± 2.4	12.4	± 4.2
Eosinophil	1.2	± 0.4	0.9	± 0.1
Basophil	0.0	± 0.0	0.0	± 0.1
Monocyte	2.6	± 0.5	2.1	± 0.1
Lymphocyte	87.5	± 2.8	84.6	± 4.1
Reticulocyte count (%)	3.37	± 1.01	3.04	± 1.14

Each value shows mean $\pm$ S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Control (vehicle: corn oil)		4-IBA (300/150 mg/kg)	
Number of females	5		3	
RBC ($\times 10^4/\mu\text{L}$)	793	± 35	768	± 58
Hemoglobin (g/dL)	14.9	± 0.6	14.5	± 0.8
Hematocrit (%)	42.4	± 1.3	40.9	± 2.6
MCV (fL)	53.5	± 1.2	53.4	± 0.8
MCH (pg)	18.8	± 0.4	18.9	± 0.5
MCHC (g/dL)	35.2	± 0.6	35.5	± 0.4
Platelet ($\times 10^4/\mu\text{L}$)	106.0	± 4.9	96.4	± 20.3
PT (sec)	12.0	± 0.3	11.7	± 0.4
APTT (sec)	22.6	± 1.4	20.7	± 1.3
WBC ($\times 10^2/\mu\text{L}$)	34.5	± 8.2	38.9	± 22.0
Differential leukocyte count (%)				
Neutrophil	17.2	± 4.5	20.7	± 7.4
Eosinophil	1.7	± 0.5	1.4	± 0.2
Basophil	0.0	± 0.0	0.0	± 0.0
Monocyte	2.7	± 0.9	3.1	± 0.2
Lymphocyte	78.4	± 3.4	74.8	± 7.8
Reticulocyte count (%)	3.46	± 0.51	4.03	± 0.84

Each value shows mean $\pm$ S.D.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg	
Number of males		5	5	5	5	
Total protein	g/dL	5.5 ± 0.2	5.4 ± 0.5	5.5 ± 0.2	5.1 ± 0.2	*
Albumin	g/dL	3.5 ± 0.1	3.4 ± 0.2	3.5 ± 0.1	3.3 ± 0.2	
A/G		1.74 ± 0.17	1.68 ± 0.17	1.71 ± 0.19	1.86 ± 0.19	
Glucose	mg/dL	142 ± 14	154 ± 6	153 ± 9	155 ± 11	
Total cholesterol	mg/dL	50 ± 9	44 ± 4	39 ± 9	36 ± 5	*
Triglyceride	mg/dL	30 ± 9	26 ± 10	21 ± 5	19 ± 7	
Phospholipid	mg/dL	82 ± 11	78 ± 6	72 ± 11	67 ± 8	
AST	U/L	56 ± 4	53 ± 4	66 ± 11	71 ± 5	**
ALT	U/L	26 ± 3	25 ± 2	31 ± 6	30 ± 7	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
LDH	U/L	73 ± 14	68 ± 18	88 ± 10	102 ± 34	
Bile acid	mg/dL	12.6 ± 10.0	12.6 ± 4.0	27.7 ± 36.2	30.1 ± 17.3	
BUN	mg/dL	15 ± 2	14 ± 1	17 ± 2	19 ± 1	**
Creatinine	mg/dL	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	
Total bilirubin	mg/dL	0.07 ± 0	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01	
ALP	U/L	347 ± 94	380 ± 128	430 ± 78	392 ± 85	
Inorganic phosphorus	mg/dL	6.0 ± 0.6	6.2 ± 0.6	6.0 ± 0.3	7.0 ± 0.6	*
Ca	mg/dL	9.5 ± 0.3	9.4 ± 0.4	9.5 ± 0.1	9.0 ± 0.3	*
Na	mEq/L	138.9 ± 0.3	139 ± 0.7	139.1 ± 0.8	138.8 ± 1.7	
K	mEq/L	4.04 ± 0.27	3.96 ± 0.16	3.99 ± 0.24	3.78 ± 0.16	
Cl	mEq/L	102.4 ± 0.8	103.5 ± 0.7	103.3 ± 1.6	103.5 ± 1.2	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of males		5	5	5
Total protein	g/dL	5.7 ± 0.4	5.3 ± 0.4	5.6 ± 0.2
Albumin	g/dL	3.5 ± 0.2	3.4 ± 0.1	3.5 ± 0.1
A/G		1.66 ± 0.11	1.78 ± 0.24	1.72 ± 0.14
Glucose	mg/dL	130 ± 17	128 ± 16	132 ± 19
Total cholesterol	mg/dL	55 ± 5	56 ± 14	51 ± 5
Triglyceride	mg/dL	19 ± 7	15 ± 5	16 ± 2
Phospholipid	mg/dL	82 ± 8	82 ± 17	78 ± 4
AST	U/L	62 ± 10	68 ± 8	58 ± 4
ALT	U/L	24 ± 3	29 ± 6	25 ± 4
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0
LDH	U/L	160 ± 128	116 ± 67	123 ± 66
Bile acid	mg/dL	9.9 ± 4.0	8.7 ± 1.3	14.2 ± 12.5
BUN	mg/dL	17 ± 2	18 ± 2	19 ± 3
Creatinine	mg/dL	0.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.1
Total bilirubin	mg/dL	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.00
ALP	U/L	274 ± 50	275 ± 38	246 ± 35
Inorganic phosphorus	mg/dL	5.9 ± 0.5	5.5 ± 0.3	6.2 ± 0.6
Ca	mg/dL	9.2 ± 0.3	8.8 ± 0.2 *	9.3 ± 0.1
Na	mEq/L	142.1 ± 0.9	142.6 ± 1	142.6 ± 0.7
K	mEq/L	3.91 ± 0.26	3.87 ± 0.16	3.75 ± 0.16
Cl	mEq/L	105.8 ± 1.3	106.6 ± 1.6	106.3 ± 1.5

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of females		5	5
Total protein	g/dL	5.7 ± 0.3	5.4 ± 0.3
Albumin	g/dL	3.7 ± 0.3	3.5 ± 0.3
A/G		1.89 ± 0.14	1.83 ± 0.25
Glucose	mg/dL	125 ± 10	140 ± 8 *
Total cholesterol	mg/dL	50 ± 3	49 ± 9
Triglyceride	mg/dL	39 ± 20	24 ± 17
Phospholipid	mg/dL	95 ± 7	102 ± 18
AST	U/L	69 ± 6	74 ± 8
ALT	U/L	39 ± 4	34 ± 6
γ-GTP	U/L	0 ± 0	0 ± 1
LDH	U/L	193 ± 110	182 ± 114
Bile acid	mg/dL	31.8 ± 18.2	16.4 ± 9.0
BUN	mg/dL	14 ± 2	11 ± 3
Creatinine	mg/dL	0.5 ± 0.1	0.5 ± 0
Total bilirubin	mg/dL	0.08 ± 0.02	0.07 ± 0.01
ALP	U/L	148 ± 29	176 ± 35
Inorganic phosphorus	mg/dL	6.3 ± 0.7	6 ± 0.6
Ca	mg/dL	9.8 ± 0.4	9.5 ± 0.3
Na	mEq/L	141.2 ± 0.7	141.2 ± 1.2
K	mEq/L	3.74 ± 0.29	3.76 ± 0.09
Cl	mEq/L	106.1 ± 1.5	107.4 ± 1.1

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 28-1-2. Biochemical findings of female rats at the end of the dosing period, non-pregnant females

Group		4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of females		5	5
Total protein	g/dL	5.3 ± 0.3	5.5 ± 0.3
Albumin	g/dL	3.6 ± 0.2	3.6 ± 0.2
A/G		2.06 ± 0.26	1.86 ± 0.12
Glucose	mg/dL	137 ± 5	136 ± 15
Total cholesterol	mg/dL	50 ± 11	63 ± 9
Triglyceride	mg/dL	15 ± 10	24 ± 17
Phospholipid	mg/dL	91 ± 18	109 ± 13
AST	U/L	63 ± 10	66 ± 10
ALT	U/L	21 ± 3	25 ± 6
γ-GTP	U/L	0 ± 1	1 ± 1
LDH	U/L	68 ± 34	117 ± 56
Bile acid	mg/dL	22.0 ± 14.0	12.0 ± 3.0
BUN	mg/dL	22 ± 11	13 ± 2
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.1
Total bilirubin	mg/dL	0.06 ± 0.01	0.05 ± 0.01
ALP	U/L	191 ± 26	215 ± 38
Inorganic phosphorus	mg/dL	5.4 ± 1.1	5.2 ± 0.7
Ca	mg/dL	9.0 ± 0.3	9.1 ± 0.2
Na	mEq/L	142.2 ± 1.1	142.9 ± 1.1
K	mEq/L	3.32 ± 0.19	3.28 ± 0.27
Cl	mEq/L	107.2 ± 2.9	106.7 ± 1.9

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 300/150 mg/kg	
Number of females		5	3	
Total protein	g/dL	5.8 ± 0.2	5.2 ± 0.5	
Albumin	g/dL	3.9 ± 0.1	3.5 ± 0.2	**
A/G		2.11 ± 0.20	2.12 ± 0.46	
Glucose	mg/dL	136 ± 6	142 ± 5	
Total cholesterol	mg/dL	58 ± 9	44 ± 13	
Triglyceride	mg/dL	15 ± 5	16 ± 8	
Phospholipid	mg/dL	104 ± 15	84 ± 19	
AST	U/L	56 ± 7	61 ± 11	
ALT	U/L	19 ± 4	21 ± 6	
γ-GTP	U/L	0 ± 0	1 ± 1	
LDH	U/L	68 ± 29	53 ± 10	
Bile acid	mg/dL	20.7 ± 17.5	27.7 ± 29.6	
BUN	mg/dL	13 ± 1	14 ± 3	
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1	
Total bilirubin	mg/dL	0.09 ± 0.02	0.07 ± 0.02	
ALP	U/L	200 ± 51	200 ± 27	
Inorganic phosphorus	mg/dL	5.2 ± 0.9	6.3 ± 0.7	
Ca	mg/dL	9.9 ± 0.2	9.1 ± 0.4	*
Na	mEq/L	142.1 ± 1.3	140.1 ± 1.6	
K	mEq/L	3.73 ± 0.42	3.78 ± 0.31	
Cl	mEq/L	106.7 ± 2.1	105 ± 3	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)	4-IBA 300/150 mg/kg	
Number of females		5	3	
Total protein	g/dL	6 ± 0.2	5.6 ± 0.1	*
Albumin	g/dL	4 ± 0.2	3.7 ± 0.2	
A/G		1.95 ± 0.23	1.98 ± 0.24	
Glucose	mg/dL	114 ± 10	98 ± 8	
Total cholesterol	mg/dL	60 ± 7	61 ± 12	
Triglyceride	mg/dL	16 ± 8	10 ± 3	
Phospholipid	mg/dL	107 ± 11	101 ± 14	
AST	U/L	56 ± 9	62 ± 7	
ALT	U/L	20 ± 3	22 ± 4	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	56 ± 13	63 ± 23	
Bile acid	mg/dL	14.6 ± 8.3	15.1 ± 8.7	
BUN	mg/dL	19 ± 3	19 ± 1	
Creatinine	mg/dL	0.7 ± 0.1	0.7 ± 0.1	
Total bilirubin	mg/dL	0.08 ± 0.01	0.07 ± 0.02	
ALP	U/L	127 ± 36	170 ± 45	
Inorganic phosphorus	mg/dL	3.9 ± 0.8	5.1 ± 0.3	
Ca	mg/dL	9.1 ± 0.3	9.1 ± 0.2	
Na	mEq/L	142.1 ± 1	141.4 ± 0.6	
K	mEq/L	3.54 ± 0.3	3.69 ± 0.46	
Cl	mEq/L	108.4 ± 1.3	106.6 ± 2.3	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 30 mg/kg		4-IBA 100 mg/kg		4-IBA 300/150 mg/kg	
Number of males		7		12		7		7	
Body weight	(g)	470.6	± 29.0	469.4	± 32.9	465.3	± 38.5	434.5	± 28.2
Brain	(mg)	2020.4	± 55.8	2025.9	± 77.4	1958.9	± 37.8	1983.2	± 46.5
	(mg/g)	4.310	± 0.326	4.334	± 0.325	4.237	± 0.381	4.577	± 0.246
Thymus	(mg)	366.5	± 51.2	270.6	± 75.0 *	266.9	± 66.8 *	230.1	± 69.6 **
	(mg/g)	0.783	± 0.132	0.575	± 0.146 *	0.578	± 0.148 *	0.528	± 0.151 **
Heart	(mg)	1423.3	± 144.4	1400.9	± 80.2	1366.5	± 143.8	1320.5	± 99.9
	(mg/g)	3.020	± 0.160	2.995	± 0.226	2.946	± 0.301	3.039	± 0.140
Liver	(mg)	12516.5	± 1061.8	13254.5	± 1511.8	15555.7	± 919.5 **	16230.5	± 880.4 **
	(mg/g)	26.619	± 1.954	28.187	± 1.832	33.548	± 2.321 **	37.464	± 2.879 **
Kidney (R)	(mg)	1484.4	± 137.2	1535.8	± 111.9	1552.3	± 175.9	1594.1	± 131.3
	(mg/g)	3.157	± 0.261	3.285	± 0.305	3.338	± 0.278	3.672	± 0.254 **
Kidney (L)	(mg)	1492.8	± 154.4	1575.6	± 115.6	1537.0	± 171.3	1562.8	± 115.1
	(mg/g)	3.171	± 0.239	3.369	± 0.296	3.303	± 0.243	3.599	± 0.203 *
Kidneys	(mg)	2977.1	± 286.9	3111.4	± 217.0	3089.3	± 344.3	3156.9	± 241.9
	(mg/g)	6.328	± 0.488	6.653	± 0.585	6.641	± 0.512	7.271	± 0.446 **
Spleen	(mg)	770.4	± 142.1	783.7	± 152.3	850.2	± 202.9	751.8	± 122.8
	(mg/g)	1.636	± 0.269	1.677	± 0.354	1.821	± 0.356	1.730	± 0.240
Testis (R)	(mg)	1493.3	± 419.4	1630.8	± 168.5	1730.1	± 110.8	940.3	± 171.5
	(mg/g)	3.149	± 0.845	3.487	± 0.405	3.735	± 0.347	2.166	± 0.389 **
Testis (L)	(mg)	1490.5	± 369.2	1608.1	± 204.0	1705.2	± 129.3	958.7	± 183.4 **
	(mg/g)	3.150	± 0.741	3.438	± 0.468	3.683	± 0.390	2.208	± 0.416 **
Testes	(mg)	2983.7	± 786.8	3239.0	± 365.1	3435.3	± 238.1	1899.0	± 352.1
	(mg/g)	6.300	± 1.582	6.925	± 0.858	7.418	± 0.734	4.374	± 0.798 **
Epididymis (R)	(mg)	564.4	± 140.6	614.2	± 55.2	727.4	± 170.3	465.7	± 60.1
	(mg/g)	1.189	± 0.257	1.319	± 0.188	1.561	± 0.332 *	1.076	± 0.154
Epididymis (L)	(mg)	547.0	± 124.2	603.0	± 62.5	761.6	± 137.4 **	446.5	± 59.1
	(mg/g)	1.155	± 0.232	1.295	± 0.192	1.639	± 0.281 **	1.032	± 0.157
Epididymides	(mg)	1111.4	± 263.0	1217.2	± 111.9	1489.0	± 300.8	912.2	± 108.7
	(mg/g)	2.344	± 0.485	2.614	± 0.371	3.200	± 0.596 **	2.108	± 0.290
Prostate, ventral	(mg)	586.7	± 108.6	558.9	± 95.0	521.9	± 117.8	516.4	± 88.4
	(mg/g)	1.241	± 0.175	1.194	± 0.209	1.135	± 0.314	1.187	± 0.177
Seminal vesicles	(mg)	1577.1	± 289.8	1716.4	± 280.2	1463.1	± 158.0	1509.2	± 124.8
	(mg/g)	3.356	± 0.618	3.684	± 0.716	3.166	± 0.463	3.481	± 0.305
Thyroid gland	(mg)	20.1	± 2.6	21.5	± 3.9	20.1	± 3.6	22.5	± 3.6
	(mg/g)	0.043	± 0.005	0.046	± 0.009	0.043	± 0.008	0.052	± 0.007

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 30 mg/kg		4-IBA 100 mg/kg		4-IBA 300/150 mg/kg	
Number of males		7		12		7		7	
Body weight	(g)	470.6	± 29.0	469.4	± 32.9	465.3	± 38.5	434.5	± 28.2
Adrenal gland (R)	(mg)	22.7	± 4.9	23.4	± 2.9	23.1	± 2.2	22.3	± 4.0
	(mg/g)	0.048	± 0.009	0.050	± 0.008	0.050	± 0.004	0.051	± 0.009
Adrenal gland (L)	(mg)	24.6	± 6.5	24.1	± 2.4	24.3	± 2.7	23.5	± 4.3
	(mg/g)	0.052	± 0.012	0.052	± 0.006	0.052	± 0.005	0.054	± 0.010
Adrenal glands	(mg)	47.3	± 11.3	47.5	± 4.3	47.4	± 4.6	45.7	± 8.0
	(mg/g)	0.100	± 0.020	0.102	± 0.013	0.102	± 0.009	0.106	± 0.018

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 100 mg/kg		4-IBA 300/150 mg/kg	
Number of males		5		5		5	
Body weight	(g)	521.0	± 35.9	462.3	± 36.6 *	455.1	± 31.4 *
Brain	(mg)	2068.4	± 74.7	1972.6	± 73.7	1922.0	± 65.6 *
	(mg/g)	3.986	± 0.334	4.283	± 0.287	4.247	± 0.442
Thymus	(mg)	297.1	± 102.8	236.5	± 61.2	311.5	± 76.3
	(mg/g)	0.578	± 0.226	0.517	± 0.149	0.681	± 0.140
Heart	(mg)	1458.0	± 40.0	1354.5	± 66.5 *	1329.5	± 36.9 **
	(mg/g)	2.806	± 0.144	2.948	± 0.323	2.930	± 0.177
Liver	(mg)	13516.2	± 1595.7	11619.0	± 1102.5	11739.5	± 1028.9
	(mg/g)	25.878	± 1.312	25.169	± 2.020	25.795	± 1.331
Kidney (R)	(mg)	1596.2	± 25.9	1494.2	± 66.2 *	1399.8	± 80.9 **
	(mg/g)	3.076	± 0.230	3.240	± 0.145	3.081	± 0.175
Kidney (L)	(mg)	1606.7	± 32.3	1544.8	± 94.3	1460.6	± 167.1
	(mg/g)	3.092	± 0.155	3.349	± 0.176	3.212	± 0.347
Kidneys	(mg)	3203.0	± 25.4	3039.0	± 158.8	2860.4	± 240.7 *
	(mg/g)	6.168	± 0.378	6.589	± 0.314	6.293	± 0.494
Spleen	(mg)	879.2	± 59.7	747.4	± 82.3	711.9	± 121.4 *
	(mg/g)	1.693	± 0.156	1.616	± 0.125	1.561	± 0.199
Testis (R)	(mg)	1673.1	± 154.1	1692.9	± 107.2	811.5	± 172.6 **
	(mg/g)	3.221	± 0.349	3.671	± 0.231	1.796	± 0.452 **
Testis (L)	(mg)	1667.1	± 133.2	1681.8	± 84.6	797.5	± 186.1 **
	(mg/g)	3.208	± 0.299	3.648	± 0.219	1.776	± 0.535 **
Testes	(mg)	3340.1	± 284.6	3374.8	± 186.6	1609.1	± 338.6 **
	(mg/g)	6.429	± 0.645	7.319	± 0.437	3.572	± 0.959 **
Epididymis (R)	(mg)	646.0	± 76.6	703.3	± 201.7	461.3	± 59.8 *
	(mg/g)	1.241	± 0.140	1.532	± 0.471	1.019	± 0.161
Epididymis (L)	(mg)	637.7	± 58.5	697.4	± 147.5	460.8	± 82.4 *
	(mg/g)	1.227	± 0.126	1.524	± 0.395	1.023	± 0.227
Epididymides	(mg)	1283.7	± 133.4	1400.7	± 243.6	922.1	± 135.3 *
	(mg/g)	2.468	± 0.260	3.057	± 0.651	2.042	± 0.378
Prostate, ventral	(mg)	583.3	± 179.7	696.0	± 111.4	752.3	± 166.6
	(mg/g)	1.118	± 0.351	1.508	± 0.222	1.656	± 0.364
Seminal vesicles	(mg)	1599.5	± 326.6	1990.3	± 319.5	1685.9	± 206.6
	(mg/g)	3.070	± 0.621	4.319	± 0.732 *	3.703	± 0.382
Thyroid gland	(mg)	20.3	± 3.7	16.7	± 3.4	21.2	± 6.6
	(mg/g)	0.039	± 0.007	0.036	± 0.006	0.046	± 0.014

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 100 mg/kg		4-IBA 300/150 mg/kg	
Number of males		5		5		5	
Body weight	(g)	521.0	± 35.9	462.3	± 36.6 *	455.1	± 31.4 *
Adrenal gland (R)	(mg)	25.5	± 2.5	23.4	± 3.4	19.3	± 5.4
	(mg/g)	0.049	± 0.004	0.051	± 0.005	0.043	± 0.013
Adrenal gland (L)	(mg)	26.6	± 1.7	25.5	± 4.0	23.4	± 4.0
	(mg/g)	0.051	± 0.004	0.055	± 0.006	0.052	± 0.012
Adrenal glands	(mg)	52.0	± 3.8	48.9	± 7.2	42.7	± 9.3
	(mg/g)	0.100	± 0.008	0.105	± 0.010	0.095	± 0.025

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 30 mg/kg	
Number of females		11		9	
Body weight	(g)	306.7	± 29.6	289.2	± 26.9
Brain	(mg)	1894.4	± 58.8	1888.9	± 68.2
	(mg/g)	6.222	± 0.546	6.581	± 0.634
Thymus	(mg)	169.4	± 34.0	136.2	± 61.4
	(mg/g)	0.553	± 0.106	0.458	± 0.183
Heart	(mg)	986.2	± 80.9	939.9	± 47.8
	(mg/g)	3.228	± 0.262	3.266	± 0.223
Liver	(mg)	9826.4	± 767.8	11348.7	± 1556.3 *
	(mg/g)	32.150	± 2.117	39.405	± 5.657 **
Kidney (R)	(mg)	959.1	± 92.6	956.9	± 147.1
	(mg/g)	3.135	± 0.227	3.314	± 0.454
Kidney (L)	(mg)	933.7	± 88.2	913.2	± 123.8
	(mg/g)	3.055	± 0.254	3.160	± 0.332
Kidneys	(mg)	1892.8	± 177.4	1870.1	± 266.5
	(mg/g)	6.190	± 0.470	6.473	± 0.773
Spleen	(mg)	706.7	± 108.5	637.8	± 134.3
	(mg/g)	2.304	± 0.282	2.199	± 0.372
Ovary (R)	(mg)	57.6	± 11.2	53.0	± 6.4
	(mg/g)	0.188	± 0.029	0.186	± 0.035
Ovary (L)	(mg)	52.0	± 6.4	49.8	± 9.8
	(mg/g)	0.169	± 0.010	0.174	± 0.042
Ovaries	(mg)	109.6	± 16.3	102.8	± 9.7
	(mg/g)	0.357	± 0.035	0.360	± 0.060
Uterus	(mg)	618.5	± 82.2	641.7	± 103.1
	(mg/g)	2.032	± 0.318	2.214	± 0.249
Thyroid gland	(mg)	17.1	± 3.9	14.2	± 2.3
	(mg/g)	0.056	± 0.013	0.049	± 0.007
Adrenal gland (R)	(mg)	34.7	± 4.5	34.8	± 5.2
	(mg/g)	0.113	± 0.014	0.121	± 0.020
Adrenal gland (L)	(mg)	37.0	± 5.1	37.2	± 4.3
	(mg/g)	0.121	± 0.014	0.129	± 0.017
Adrenal glands	(mg)	71.7	± 9.4	72.0	± 9.3
	(mg/g)	0.234	± 0.028	0.251	± 0.037

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 30-1-2. Organ weights of female rats at the end of the dosing period, non-pregnant females

Group		Control (vehicle: corn oil)	4-IBA 30 mg/kg	4-IBA 100 mg/kg	4-IBA 300/150 mg/kg
Number of females		1	2	12	8
Body weight	(g)	276.3 ±	280.1 ±	271.0 ± 17.0	261.5 ± 27.8
Brain	(mg)	1968.2 ±	1854.0 ±	1877.7 ± 67.0	1853.7 ± 81.6
	(mg/g)	7.123 ±	6.634 ±	6.951 ± 0.450	7.138 ± 0.580
Thymus	(mg)	335.7 ±	265.2 ±	253.4 ± 48.0	264.1 ± 42.6
	(mg/g)	1.215 ±	0.944 ±	0.936 ± 0.171	1.019 ± 0.177
Heart	(mg)	983.9 ±	893.8 ±	845.7 ± 81.6	873.1 ± 131.6
	(mg/g)	3.561 ±	3.185 ±	3.121 ± 0.220	3.338 ± 0.340
Liver	(mg)	7876.8 ±	8750.7 ±	9908.3 ± 869.3	10411.5 ± 1359.0
	(mg/g)	28.508 ±	31.256 ±	36.547 ± 1.845	39.781 ± 2.231
Kidney (R)	(mg)	962.5 ±	990.2 ±	982.5 ± 117.8	965.8 ± 167.5
	(mg/g)	3.484 ±	3.547 ±	3.624 ± 0.347	3.692 ± 0.457
Kidney (L)	(mg)	915.1 ±	963.6 ±	951.4 ± 98.1	934.9 ± 152.8
	(mg/g)	3.312 ±	3.449 ±	3.512 ± 0.301	3.572 ± 0.377
Kidneys	(mg)	1877.6 ±	1953.8 ±	1933.9 ± 213.2	1900.7 ± 318.3
	(mg/g)	6.796 ±	6.995 ±	7.136 ± 0.634	7.265 ± 0.826
Spleen	(mg)	830.2 ±	563.3 ±	534.9 ± 67.4	577.1 ± 125.9
	(mg/g)	3.005 ±	2.010 ±	1.982 ± 0.277	2.191 ± 0.302
Ovary (R)	(mg)	53.7 ±	49.6 ±	41.7 ± 6.1	40.6 ± 8.5
	(mg/g)	0.194 ±	0.178 ±	0.155 ± 0.025	0.154 ± 0.020
Ovary (L)	(mg)	56.0 ±	52.8 ±	44.2 ± 8.4	38.2 ± 7.5
	(mg/g)	0.203 ±	0.189 ±	0.163 ± 0.027	0.145 ± 0.020
Ovaries	(mg)	109.7 ±	102.4 ±	86.0 ± 11.8	78.8 ± 15.1
	(mg/g)	0.397 ±	0.367 ±	0.318 ± 0.041	0.300 ± 0.035
Uterus	(mg)	462.3 ±	782.2 ±	550.2 ± 231.5	517.8 ± 211.3
	(mg/g)	1.673 ±	2.796 ±	2.024 ± 0.819	1.975 ± 0.820
Thyroid gland	(mg)	22.0 ±	16.7 ±	16.3 ± 4.7	14.3 ± 4.6
	(mg/g)	0.080 ±	0.060 ±	0.060 ± 0.018	0.054 ± 0.017
Adrenal gland (R)	(mg)	28.2 ±	36.4 ±	28.0 ± 3.3	26.9 ± 3.8
	(mg/g)	0.102 ±	0.130 ±	0.104 ± 0.015	0.103 ± 0.013
Adrenal gland (L)	(mg)	29.5 ±	39.7 ±	29.2 ± 3.6	29.1 ± 4.6
	(mg/g)	0.107 ±	0.142 ±	0.108 ± 0.015	0.112 ± 0.016
Adrenal glands	(mg)	57.7 ±	76.0 ±	57.3 ± 6.6	56.1 ± 8.0
	(mg/g)	0.209 ±	0.272 ±	0.212 ± 0.029	0.215 ± 0.027

Each value shows mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 300/150 mg/kg	
Number of females		5		3	
Body weight	(g)	291.9 ±	27.6	274.3 ±	23.6
Brain	(mg)	1950.8 ±	31.5	1821.4 ±	64.2 **
	(mg/g)	6.725 ±	0.559	6.663 ±	0.423
Thymus	(mg)	317.0 ±	58.6	275.3 ±	72.0
	(mg/g)	1.083 ±	0.139	0.994 ±	0.175
Heart	(mg)	945.7 ±	65.7	876.5 ±	36.6
	(mg/g)	3.266 ±	0.415	3.214 ±	0.342
Liver	(mg)	7310.6 ±	527.1	10841.4 ±	169.7 **
	(mg/g)	25.091 ±	0.734	39.691 ±	2.838 **
Kidney (R)	(mg)	885.0 ±	93.3	953.2 ±	54.2
	(mg/g)	3.030 ±	0.091	3.482 ±	0.140 **
Kidney (L)	(mg)	857.6 ±	108.2	947.4 ±	80.1
	(mg/g)	2.931 ±	0.109	3.455 ±	0.062 **
Kidneys	(mg)	1742.6 ±	201.0	1900.5 ±	128.9
	(mg/g)	5.960 ±	0.186	6.937 ±	0.127 **
Spleen	(mg)	594.5 ±	67.2	567.1 ±	123.7
	(mg/g)	2.038 ±	0.159	2.054 ±	0.315
Ovary (R)	(mg)	51.1 ±	9.0	43.6 ±	14.4
	(mg/g)	0.175 ±	0.029	0.158 ±	0.044
Ovary (L)	(mg)	58.1 ±	21.3	41.2 ±	10.3
	(mg/g)	0.196 ±	0.057	0.149 ±	0.027
Ovaries	(mg)	109.2 ±	29.1	84.8 ±	20.1
	(mg/g)	0.372 ±	0.076	0.307 ±	0.048
Uterus	(mg)	554.7 ±	265.6	518.5 ±	125.9
	(mg/g)	1.936 ±	0.997	1.880 ±	0.376
Thyroid gland	(mg)	15.1 ±	3.2	16.5 ±	2.6
	(mg/g)	0.053 ±	0.015	0.060 ±	0.005
Adrenal gland (R)	(mg)	29.3 ±	2.1	33.5 ±	4.4
	(mg/g)	0.101 ±	0.015	0.123 ±	0.024
Adrenal gland (L)	(mg)	30.8 ±	2.7	36.3 ±	2.8 *
	(mg/g)	0.107 ±	0.018	0.134 ±	0.022
Adrenal glands	(mg)	60.1 ±	4.8	69.9 ±	6.4 *
	(mg/g)	0.208 ±	0.033	0.257 ±	0.043

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group		Control (vehicle: corn oil)		4-IBA 300/150 mg/kg	
Number of females		5		3	
Body weight	(g)	306.3	± 27.8	259.9	± 25.5
Brain	(mg)	1919.1	± 63.6	1853.5	± 24.6
	(mg/g)	6.304	± 0.565	7.174	± 0.653
Thymus	(mg)	263.3	± 35.1	353.2	± 27.0 **
	(mg/g)	0.861	± 0.106	1.374	± 0.240 **
Heart	(mg)	968.5	± 126.7	816.1	± 48.4
	(mg/g)	3.163	± 0.324	3.161	± 0.361
Liver	(mg)	7487.5	± 606.2	7075.6	± 898.4
	(mg/g)	24.506	± 1.764	27.219	± 2.031
Kidney (R)	(mg)	909.1	± 71.4	872.6	± 64.4
	(mg/g)	2.977	± 0.222	3.370	± 0.266
Kidney (L)	(mg)	892.0	± 93.9	909.7	± 216.2
	(mg/g)	2.917	± 0.260	3.492	± 0.675
Kidneys	(mg)	1801.0	± 165.0	1782.3	± 280.5
	(mg/g)	5.893	± 0.475	6.862	± 0.852
Spleen	(mg)	535.8	± 32.0	506.4	± 50.0
	(mg/g)	1.764	± 0.216	1.949	± 0.013
Ovary (R)	(mg)	49.2	± 4.8	40.4	± 6.4
	(mg/g)	0.162	± 0.026	0.158	± 0.042
Ovary (L)	(mg)	50.8	± 4.7	43.7	± 14.9
	(mg/g)	0.167	± 0.027	0.172	± 0.070
Ovaries	(mg)	100.0	± 9.2	84.0	± 20.1
	(mg/g)	0.330	± 0.053	0.330	± 0.108
Uterus	(mg)	743.7	± 372.4	414.8	± 56.9
	(mg/g)	2.491	± 1.339	1.609	± 0.279
Thyroid gland	(mg)	20.5	± 1.9	13.7	± 1.4 **
	(mg/g)	0.067	± 0.006	0.053	± 0.010
Adrenal gland (R)	(mg)	28.2	± 9.3	28.1	± 1.4
	(mg/g)	0.093	± 0.033	0.109	± 0.012
Adrenal gland (L)	(mg)	28.9	± 13.8	37.1	± 12.4
	(mg/g)	0.095	± 0.047	0.141	± 0.039
Adrenal glands	(mg)	57.1	± 23.0	65.2	± 11.6
	(mg/g)	0.189	± 0.080	0.250	± 0.030

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Findings	Group	4-IBA		4-IBA		4-IBA		4-IBA	
	Dose(mg/kg)	0		30		100		300/150	
	Grade	-	P	-	P	-	P	-	P
Thyroid gland									
Enlargement		7	0	12	0	7	0	6	1
Liver									
Discoloration, pale colored		7	0	12	0	7	0	5	2
Enlargement		7	0	11	1	4	3	1	6
Kidney									
Enlargement		7	0	12	0	7	0	6	1
Spleen									
Enlargement		7	0	12	0	6	1	6	1
Adrenal gland									
Small, bilateral		6	1	12	0	7	0	7	0
Testis									
Edematous, bilateral		6	1	12	0	7	0	2	5
Enlargement, bilateral		7	0	11	1	6	1	7	0
Small, bilateral		6	1	12	0	7	0	0	7
Epididymis									
Enlargement		7	0	12	0	6	1	6	1
Nodule, whitish, caudal, bilateral/unilateral		7	0	12	0	5	2	6	1
Small, bilateral		7	0	12	0	7	0	4	3

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	4-IBA		4-IBA		4-IBA	
	Dose(mg/kg)	0		100		300/150	
	Grade	-	P	-	P	-	P
Testis							
Edematous, bilateral		5	0	5	0	2	3
Small, bilateral		5	0	5	0	0	5
Epididymis							
Edematous, bilateral		5	0	5	0	4	1
Nodule, whitish, caudal, bilateral/unilateral		5	0	3	2	5	0
Small, bilateral		5	0	5	0	1	4

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 32-1-1. Macroscopic findings of female rats, dead/moribund females

Findings	Group Dose(mg/kg) Grade	4-IBA 300/150		4-IBA, satellite 300/150	
		-	P	-	P
Pituitary gland					
Discoloration, dark colored		4	0	3	1
Thyroid gland					
Discoloration, dark reddish		3	1	3	1
Thymus					
Small		1	3	1	3
Discoloration, dark reddish		2	2	4	0
Lung					
Dark reddish area		2	2	2	2
Discoloration, dark reddish		3	1	4	0
Liver					
Enlargement		0	4	0	4
Discoloration, pale colored		3	1	2	2
Accentuated lobular pattern		3	1	4	0
Pale colored spot		3	1	4	0
Stomach					
Thinning, mucosa		3	1	4	0
Small intestine					
Retention, watery content		4	0	3	1
Retention, with black content		4	0	2	2
Kidney					
Enlargement, bilateral		3	1	3	1
Discoloration, dark reddish, papilla		3	1	4	0
Dark colored area, bilateral		4	0	3	1
Rough surface, bilateral		4	0	3	1
Spleen					
Small		0	4	0	4
Discoloration, pale colored		3	1	2	2
Adrenal gland					
Enlargement, bilateral		0	4	2	2
Uterus					
Discoloration, dark colored		3	1	4	0
Hair					
Soiled fur, perineal/perinasal area/region		2	2	2	2
Notes) -: No abnormal changes P: Non-graded change					
Numerals represent the number of animals.					

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 32-1-2. Macroscopic findings of female rats at the end of the dosing period, dams

Findings	Group	4-IBA		4-IBA	
	Dose(mg/kg)	0		30	
	Grade	-	P	-	P
Thymus					
Small		11	0	7	2
Stomach					
Dark colored spot/area, mucosa, glandular stomach		11	0	8	1
Skin					
Nodule, subcutaneous		10	1	8	1

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 32-1-3. Macroscopic findings of female rats at the end of the dosing period, non-pregnant females

Findings	Group	4-IBA		4-IBA		4-IBA		4-IBA	
	Dose(mg/kg)	0		30		100		300/150	
	Grade	-	P	-	P	-	P	-	P
Liver									
Accentuated lobular pattern		1	0	2	0	11	1	2	6
Discoloration, pale colored		1	0	2	0	9	3	4	4
Enlargement		1	0	2	0	9	3	0	8
Stomach									
Dark colored spot/area,		1	0	2	0	8	4	7	1
mucosa, glandular stomach									
Edematous, mucosa, forestomach		1	0	2	0	12	0	6	2
Recessed area,									
mucosa, glandular stomach		1	0	2	0	11	1	8	0

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	4-IBA		4-IBA	
	Dose(mg/kg)	0		300/150	
	Grade	-	P	-	P
Liver					
Discoloration, pale colored		5	0	2	1
Enlargement		5	0	0	3
Stomach					
Dark colored spot/area		5	0	2	1
mucosa, glandular stomach					
Edematous, mucosa, forestomach		5	0	2	1

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	4-IBA		4-IBA	
	Dose(mg/kg)	0		300/150	
	Grade	-	P	-	P
Adrenal gland					
Small		4	1	3	0

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

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-1. Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg) Grade	4-IBA 0						4-IBA 30						4-IBA 100						4-IBA 300/150									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							0						5	0						5	5						2
Spinal cord		5							0						5	0						5	5						2
Pituitary gland																													
Dilatation, Rathke's pouch		4					1		0					0	5	0			0	5		5					0	2	
Submandibular gland		5							0						5	0						5	5						2
Sublingual gland		5							0						5	0						5	5						2
Lymph node, submandibular		5							0						5	0						5	5						2
Thyroid gland																													
Ultimobranchial rest		4					1		0					0	5	0			0	5		4					1	2	
Parathyroid gland		5							0						5	0						5	5						2
Thymus		5							0						5	0						5	5						2
Heart																													
Degeneration/fibrosis, myocardial, focal		3	2	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	4	1	0	0	0		2
Trachea		5							0						5	0						5	5						2
Lung																													
Accumulation, foam cell, alveolar		2	3	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	3	2	0	0	0		2
Hemorrhage, focal		4	1	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	5	0	0	0	0		2
Metaplasia, osseous, focal		4	1	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	5	0	0	0	0		2
Mineralization, arterial wall		3	2	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	5	0	0	0	0		2
Bronchus		5							0						5	0						5	5						2
Liver																													
Fatty change, hepatocyte, periportal		0	3	2	0	0			0	5	0	0	0			1	4	0	0	0			0	6	1	0	0		
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		5	0	0	0	0			5	0	0	0	0			0	4	1	0	0		**##	0	2	5	0	0		**##
Microgranuloma		4	1	0	0	0			3	2	0	0	0			0	5	0	0	0		#	0	6	1	0	0		*,#
Necrosis, focal, subserosa		5	0	0	0	0			5	0	0	0	0			5	0	0	0	0			6	1	0	0	0		
Single cell necrosis		5	0	0	0	0			5	0	0	0	0			1	4	0	0	0		#	3	2	2	0	0		
Pancreas																													
Cellular infiltration, lymphocyte, interstitial		4	1	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	5	0	0	0	0		2

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 30							4-IBA 100							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Stomach		5							0						5	0						5	5					2	
Duodenum		5							0						5	0						5	5					2	
Jejunum		5							0						5	0						5	5					2	
Ileum		5							0						5	0						5	5					2	
Cecum		5							0						5	0						5	5					2	
Colon		5							0						5	0						5	5					2	
Rectum		5							0						5	0						5	5					2	
Lymph node, mesenteric		5							0						5	0						5	5					2	
Spleen																													
Deposit, pigment, brown		0	3	2	0	0			0	3	2	0	0			0	0	5	0	0			0	0	3	2	0		2
Hematopoiesis, extramedullary		0	1	4	0	0			0	1	4	0	0			0	0	5	0	0			0	1	4	0	0		2
Kidney																													
Basophilic tubule, cortex		3	2	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	4	1	0	0	0		2
Mineralization, medulla		4	1	0	0	0			0	0	0	0	0		5	0	0	0	0	0		5	4	1	0	0	0		2
Urinary bladder		5							0						5	0						5	5					2	
Adrenal gland		5							0						5	0						5	5					2	

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg) Grade	4-IBA 0						4-IBA 30						4-IBA 100						4-IBA 300/150									
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Testis																													
Atrophy, seminiferous tubule, focal bilateral		4	0	0	1	0			4	1	0	0	0			5	0	0	0	0			0	0	4	3	0		#
Decrease, elongated spermatid, seminiferous tubule, bilateral		5	0	0	0	0			5	0	0	0	0			5	0	0	0	0			0	0	5	2	0		**,##
Hyperplasia, Leydig cell, interstitial, bilateral		4	0	1	0	0			5	0	0	0	0			5	0	0	0	0			0	7	0	0	0		#
Multinucleated giant cell, seminiferous tubule, bilateral		4	0	1	0	0			5	0	0	0	0			5	0	0	0	0			1	2	4	0	0		#
Epididymis																													
Cell debris, lumen, bilateral		4	0	0	1	0			4	1	0	0	0			0	5	0	0	0	#		0	0	3	4	0		*,#
Decrease, sperm, lumen bilateral		5	0	0	0	0			5	0	0	0	0			0	2	3	0	0	**,##		0	0	0	7	0		**,##
Granuloma, spermatic, caudal, bilateral/unilateral		5	0	0	0	0			5	0	0	0	0			2	0	1	2	0			5	0	0	2	0		
Prostate																													
Cellular infiltration, lymphocyte, interstitial		2	2	1	0	0			0	0	0	0	0	5		0	0	0	0	0	5		1	4	0	0	0		2
Seminal vesicle		5							0					5		0					5		5						2
Coagulating gland		5							0					5		0					5		5						2
Eyeball		5							0					5		0					5		5						2
Harderian gland																													
Cellular infiltration, lymphocyte		4	1	0	0	0			0	0	0	0	0	5		0	0	0	0	0	5		5	0	0	0	0		2
Sciatic nerve		5							0					5		0					5		5						2
Skeletal muscle		5							0					5		0					5		5						2
Femur		5							0					5		0					5		5						2
Marrow, femur		5							0					5		0					5		5						2

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

*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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-2. Histopathological findings of male rats at the end of the dosing period, recovery group

Findings	Group Dose(mg/kg) Grade	4-IBA 0						4-IBA 100						4-IBA 300/150								
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						5	0						5
Spinal cord		0						5	0						5	0						5
Pituitary gland		0						5	0						5	0						5
Submandibular gland		0						5	0						5	0						5
Sublingual gland		0						5	0						5	0						5
Lymph node, submandibular		0						5	0						5	0						5
Thyroid gland		0						5	0						5	0						5
Parathyroid gland		0						5	0						5	0						5
Thymus		0						5	0						5	0						5
Heart		0						5	0						5	0						5
Trachea		0						5	0						5	0						5
Lung		0						5	0						5	0						5
Bronchus		0						5	0						5	0						5
Liver																						
Fatty change, hepatocyte, periportal		1	3	1	0	0			2	3	0	0	0			5	0	0	0	0		#
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		5	0	0	0	0			4	1	0	0	0			0	3	2	0	0		**,##
Microgranuloma		1	4	0	0	0			5	0	0	0	0		#	5	0	0	0	0		#
Necrosis, focal, subserosa		5	0	0	0	0			5	0	0	0	0			4	1	0	0	0		
Pancreas		0						5	0						5	0						5

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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-2.(continued). Histopathological findings of male rats at the end of the dosing period, recovery group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 100							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Stomach		0						5	0						5	0						5
Duodenum		0						5	0						5	0						5
Jejunum		0						5	0						5	0						5
Ileum		0						5	0						5	0						5
Cecum		0						5	0						5	0						5
Colon		0						5	0						5	0						5
Rectum		0						5	0						5	0						5
Lymph node, mesenteric		0						5	0						5	0						5
Spleen																						
Deposit, pigment, brown		0	0	3	2	0			0	0	2	3	0			0	0	4	1	0		
Hematopoiesis, extramedullary		0	1	4	0	0			0	1	4	0	0			0	1	4	0	0		
Kidney		0						5	0						5	0						5
Urinary bladder		0						5	0						5	0						5
Adrenal gland		0						5	0						5	0						5

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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 33-2.(continued). Histopathological findings of male rats at the end of the dosing period, recovery group

Findings	Group	4-IBA							4-IBA							4-IBA						
	Dose(mg/kg)	0							100							300/150						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Testis																						
Atrophy, seminiferous tubule, focal bilateral		5	0	0	0	0			5	0	0	0	0			0	0	4	1	0	**	##
Decrease, elongated spermatid, seminiferous tubule, bilateral		5	0	0	0	0			5	0	0	0	0			0	0	2	3	0	**	##
Hyperplasia, Leydig cell, interstitial, bilateral		5	0	0	0	0			5	0	0	0	0			0	5	0	0	0	**	##
Multinucleated giant cell, seminiferous tubule, bilateral		5	0	0	0	0			5	0	0	0	0			1	4	0	0	0	#	
Epididymis																						
Cell debris, lumen, bilateral		5	0	0	0	0			0	5	0	0	0	**	##	0	0	2	3	0	**	##
Decrease, sperm, lumen bilateral		5	0	0	0	0			0	4	1	0	0	**	##	0	0	0	3	2	**	##
Granuloma, spermatic, caudal, bilateral/unilateral		4	0	1	0	0			3	0	0	2	0			5	0	0	0	0		
Prostate		0						5	0					5		0					5	
Seminal vesicle		0						5	0					5		0					5	
Coagulating gland		0						5	0					5		0					5	
Eyeball		0						5	0					5		0					5	
Harderian gland		0						5	0					5		0					5	
Sciatic nerve		0						5	0					5		0					5	
Skeletal muscle		0						5	0					5		0					5	
Femur		0						5	0					5		0					5	
Marrow, femur		0						5	0					5		0					5	

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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-1. Histopathological findings of female rats, dead/moribund females

Findings	Group Dose(mg/kg) Grade	4-IBA 300/150						4-IBA, satellite 300/150							
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		4							4						
Spinal cord		4							4						
Pituitary gland															
Remnant, rathke's pouch		4							4						
Submandibular gland															
Cellular infiltration, lymphocyte, around the artery		3	1	0	0	0			4	0	0	0	0		
Sublingual gland		4							4						
Lymph node, submandibular															
Atrophy		2	0	1	1	0			2	0	2	0	0		
Thyroid gland															
Ectopic thymic tissue		2					2		4						
Parathyroid gland		3						1	4						
Thymus															
Atrophy		2	0	0	0	2			1	0	0	1	2		
Heart															
Degeneration/fibrosis, myocardial, focal		3	1	0	0	0			2	2	0	0	0		
Trachea		4							4						
Lung															
Accumulation, foam cell, alveolus		1	3	0	0	0			2	1	1	0	0		
Mineralization, focal, arterial wall		3	1	0	0	0			4	0	0	0	0		
Bronchus		4							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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-1(continued). Histopathological findings of of female rats, dead/moribund females

Findings	Group Dose(mg/kg) Grade	4-IBA 300/150							4-IBA, satellite 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Degeneration, vacuolar, hepatocyte		0	1	2	1	0			0	2	1	1	0		
Fatty change, hepatocyte, periportal		4	0	0	0	0			3	0	1	0	0		
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		0	0	1	3	0			0	0	0	4	0		
Microgranuloma		4	0	0	0	0			3	0	1	0	0		
Pancreas		4							4						
Stomach		4							4						
Duodenum		4							4						
Jejunum		4							4						
Ileum		4							4						
Cecum		4							4						
Colon		4							4						
Rectum		4							4						
Lymph node, mesenteric															
Atrophy		1	1	2	0	0			1	0	2	1	0		
Spleen															
Decrease, red pulp		0	0	1	3	0			0	0	1	3	0		
Decrease, white pulp		0	1	3	0	0			0	1	2	1	0		
Deposit, pigment, brown		0	1	0	3	0			0	0	1	3	0		
Hematopoiesis, extramedullary		3	1	0	0	0			1	3	0	0	0		
Kidney															
Basophilic tubule, cortex		3	0	1	0	0			4	0	0	0	0		
Degeneration, vacuolar, distal/ collecting tubule		0	0	1	3	0			0	0	2	2	0		
Mineralization, C-M junction, focal		3	1	0	0	0			4	0	0	0	0		
Necrosis, papilla		3	0	1	0	0			3	1	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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-1(continued). Histopathological findings of female rats, dead/moribund females

Findings	Group Dose(mg/kg) Grade	4-IBA 300/150							4-IBA, satellite 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Urinary bladder		4							4						
Adrenal gland															
Hypertrophy, cortical cell, zona fasciculata		0	0	4	0	0			1	0	3	0	0		
Ovary															
Cyst, ovarian		4	0	0	0	0			4	0	0	0	0		
Uterus		4							4						
Vagina		4							4						
Eyeball		4							4						
Harderian gland		4							4						
Sciatic nerve		4							4						
Skeletal muscle		4							4						
Femur		4							4						
Marrow, femur															
Hematopoiesis, decreased		4	0	0	0	0			3	0	0	1	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-2. Histopathological findings of female rats at the end of the dosing period, dams

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 30						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							5						
Spinal cord		5							5						
Pituitary gland															
Remnant, Rathke's pouch		4					1		5					0	
Submandibular gland		5							5						
Sublingual gland		5							5						
Lymph node, submandibular		5							5						
Thyroid gland															
Ultimobranchial rest		3					2		5					0	
Parathyroid gland		4						1	5						
Thymus															
Atrophy		5	0	0	0	0			3	0	2	0	0		
Heart															
Degeneration/fibrosis, myocardial, focal		4	1	0	0	0			5	0	0	0	0		
Trachea		5							5						
Lung															
Accumulation, foam cell, alveolus		3	2	0	0	0			4	1	0	0	0		
Cellular infiltration, eosinophil		4	1	0	0	0			5	0	0	0	0		
Bronchus		5							5						

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-2(continued). Histopathological findings of female rats at the end of the dosing period, dams

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 30						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		5	0	0	0	0			2	3	0	0	0		
Hematopoiesis, extramedullary		4	1	0	0	0			5	0	0	0	0		
Microgranuloma		3	2	0	0	0			4	1	0	0	0		
Pancreas		5							5						
Stomach		5							5						
Duodenum		5							5						
Jejunum		5							5						
Ileum		5							5						
Cecum		5							5						
Colon		5							5						
Rectum		5							5						
Lymph node, mesenteric		5							5						
Spleen															
Deposit, pigment, brown		0	0	3	2	0			0	0	2	3	0		
Hematopoiesis, extramedullary		0	0	1	4	0			0	0	4	1	0		
Kidney															
Mineralization, C-M junction, focal		4	1	0	0	0			4	1	0	0	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-2(continued). Histopathological findings of female rats at the end of the dosing period, dams

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 30						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Urinary bladder		5							5						
Adrenal gland		5							5						
Ovary															
Cyst, ovarian		4	1	0	0	0			5	0	0	0	0		
Uterus		5							5						
Vagina		5							5						
Eyeball		5							5						
Harderian gland		5							5						
Sciatic nerve		5							5						
Skeletal muscle		5							5						
Femur		5							5						
Marrow, femur		5							5						
Mammary gland															
Cellular infiltration, inflammatory		0	0	0	1	0		4							
Hyperplasia, acinar cell, lumen/interstitial		0					1	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.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-3. Histopathological findings of female rats at the end of the dosing period, non-pregnant females

Findings	Group Dose(mg/kg) Grade	4-IBA 100							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain									5						
Spinal cord									5						
Pituitary gland									5						
Submandibular gland									5						
Sublingual gland									5						
Lymph node, submandibular									5						
Thyroid gland															
Ultimobranchial rest									3					2	
Parathyroid gland									5						
Thymus									5						
Heart															
Degeneration/fibrosis, myocardial, focal									4	1	0	0	0		
Trachea									5						
Lung															
Accumulation, foam cell, alveolus									2	3	0	0	0		
Mineralization, focal, arterial wall									4	1	0	0	0		
Bronchus									5						

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-3(continued). Histopathological findings of female rats at the end of the dosing period, non-pregnant females

Findings	Group	4-IBA							4-IBA						
	Dose(mg/kg)	100							300/150						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		1	6	2	0	0			0	5	3	0	0		
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		0	9	0	0	0			0	5	3	0	0		
Microgranuloma		8	1	0	0	0			1	3	4	0	0		
Single cell necrosis		9	0	0	0	0			2	5	1	0	0		
Pancreas															
									5						
Stomach															
Erosion, mucosa, forestomach		2	2	0	0	0			5	0	0	0	0		
Duodenum															
									5						
Jejunum															
									5						
Ileum															
									5						
Cecum															
									5						
Colon															
									5						
Rectum															
									5						
Lymph node, mesenteric															
									5						
Spleen															
Deposit, pigment, brown		0	0	1	3	0			0	0	0	5	0		
Hematopoiesis, extramedullary		0	2	2	0	0			0	1	3	1	0		
Kidney															
Degeneration, vacuolar, distal/ collecting tubule									2	2	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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-1-3(continued). Histopathological findings of female rats at the end of the dosing period, non-pregnant females

Findings	Group Dose(mg/kg) Grade	4-IBA 100							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Urinary bladder									5						
Adrenal gland															
Vacuolation, cytoplasmic, cortical cell, focal, zona fasciculata									4	0	1	0	0		
Ovary															
Cyst, ovarian									5	0	0	0	0		
Uterus									5						
Vagina									5						
Eyeball									5						
Harderian gland									5						
Sciatic nerve									5						
Skeletal muscle									5						
Femur									5						
Marrow, femur									5						

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		5							3						
Spinal cord		5							3						
Pituitary gland		5							3						
Submandibular gland		5							3						
Sublingual gland		5							3						
Lymph node, submandibular		5							3						
Thyroid gland		5							3						
Parathyroid gland		4						1	2					1	
Thymus		5							3						
Heart		5							3						
Trachea		5							3						
Lung															
Accumulation, foam cell, alveolus		5	0	0	0	0			2	1	0	0	0		
Bronchus		5							3						

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

*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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		3	2	0	0	0			0	2	1	0	0		
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		5	0	0	0	0			0	2	1	0	0	**	#
Microgranuloma		3	2	0	0	0			2	1	0	0	0		
Pancreas		5							3						
Stomach															
Edema, lamina propria mucosa, forestomach		5	0	0	0	0			2	0	1	0	0		
Erosion, mucosa, glandular stomach		5	0	0	0	0			2	1	0	0	0		
Hyperplasia, squamous cell, forestomach		5	0	0	0	0			2	1	0	0	0		
Duodenum		5							3						
Jejunum		5							3						
Ileum		5							3						
Cecum		5							3						
Colon		5							3						
Rectum		5							3						

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

*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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Lymph node, mesenteric		5							3						
Spleen															
Deposit, pigment, brown		0	0	3	2	0			0	0	1	2	0		
Hematopoiesis, extramedullary		0	1	4	0	0			0	0	3	0	0		
Kidney															
Degeneration, vacuolar, distal/ collecting tubule		5	0	0	0	0			0	2	1	0	0		** , #
Mineralization, medulla		4	1	0	0	0			3	0	0	0	0		
Urinary bladder		5							3						
Adrenal gland		5							3						
Ovary															
Cyst, ovarian		4	1	0	0	0			3	0	0	0	0		
Uterus		5							3						
Vagina		5							3						
Eyeball		5							3						
Harderian gland		5							3						
Sciatic nerve		5							3						
Skeletal muscle		5							3						
Femur		5							3						
Marrow, femur		5							3						

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

P : Non-graded change NE: Not examined

Numerals represent the number of animals.

*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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-3. Histopathological findings of female rats at the end of the dosing period, recovery group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain		0						5	0						3
Spinal cord		0						5	0						3
Pituitary gland		0						5	0						3
Submandibular gland		0						5	0						3
Sublingual gland		0						5	0						3
Lymph node, submandibular		0						5	0						3
Thyroid gland		0						5	0						3
Parathyroid gland		0						5	0						3
Thymus		0						5	0						3
Heart		0						5	0						3
Trachea		0						5	0						3
Lung		0						5	0						3
Bronchus		0						5	0						3

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the dosing period, recovery group

Findings	Group	4-IBA							4-IBA						
	Dose(mg/kg)	0							300/150						
	Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver															
Fatty change, hepatocyte, periportal		4	1	0	0	0			1	2	0	0	0		
Microgranuloma		3	2	0	0	0			3	0	0	0	0		
Pancreas		0						5	0						3
Stomach		0						5	0						3
Duodenum		0						5	0						3
Jejunum		0						5	0						3
Ileum		0						5	0						3
Cecum		0						5	0						3
Colon		0						5	0						3
Rectum		0						5	0						3
Lymph node, mesenteric		0						5	0						3
Spleen															
Deposit, pigment, brown		0	0	2	3	0			0	0	1	2	0		
Hematopoiesis, extramedullary		0	1	4	0	0			0	1	2	0	0		

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the dosing period, recovery group

Findings	Group Dose(mg/kg) Grade	4-IBA 0							4-IBA 300/150						
		-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney															
Basophilic tubule, cortex		5	0	0	0	0			2	1	0	0	0		
Mineralization, medulla		4	1	0	0	0			2	1	0	0	0		
Necrosis, papilla		5	0	0	0	0			2	1	0	0	0		
Urinary bladder		0						5	0						3
Adrenal gland		1						4	0						3
Ovary		0						5	0						3
Uterus		0						5	0						3
Vagina		0						5	0						3
Eyeball		0						5	0						3
Harderian gland		0						5	0						3
Sciatic nerve		0						5	0						3
Skeletal muscle		0						5	0						3
Femur		0						5	0						3
Marrow, femur		0						5	0						3

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

P: Non-graded change NE: Not examined

Numerals represent the number of animals.

Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Control (vehicle :corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
Number of animals examined	12	12	12	12
<u>Pre-treatment period</u>				
Number of animals showing type of cycle				
4-day cycle	10	11	9	9
4/5-day cycle	2	1	1	2
5-day cycle	0	0	2	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.2 (12)	4.0 ± 0.1 (12)	4.2 ± 0.4 (12)	4.2 ± 0.3 (12)
<u>Treatment period</u>				
Number of animals showing each type of cycle				
4-day cycle	10	7	8	3
4/5-day cycle	1	2	2	4
5-day cycle	1	2	2	2
irregular cycle	0	1	0	1
uncycle	0	0	0	1
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.2 ± 0.4 (12)	4.2 ± 0.4 (12)	5.0 ± 1.8 (10)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	1 / 12	0 / 12	2 / 11
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (10)

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Control (vehicle: corn oil)	4-IBA (30 mg/kg)	4-IBA (100 mg/kg)	4-IBA (300/150 mg/kg)
Number of mated pairs [A]	12	12	12	11
Number of copulated pairs [B]	12	12	12	11
Copulation index [(B/A) × 100,%]	100.0	100.0	100.0	100.0
Number of fertile males [C]	11	10	0	0
Fertility index [(C/B) × 100,%]	91.7	83.3	0.0 **	0.0 **
Pairing days until copulation ; Mean±S.D.(N)	3.2 ± 1.0 (12)	3.2 ± 1.1 (12)	2.8 ± 1.3 (12)	1.9 ± 0.9 * (10)

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 37. Observation of offspring (F₁)

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams	11	10
Gestation length (days)		
Mean ± S.D. per dam	22.0 ± 0.0	21.8 ± 0.6
Number of corpora lutea		
Total	181	153
Mean ± S.D. per dam	16.5 ± 2.0	15.3 ± 1.6
Number of implantation scars		
Total	167	149
Mean ± S.D. per dam	15.2 ± 3.3	14.9 ± 1.8
Implantation index (%) ^{a)}	92.6 ± 17.3	97.4 ± 4.5
Delivery index (dams,%) ^{b)}	100.0	90.0
Number of offspring at birth		
Total	158	129
Mean ± S.D. per dam	14.4 ± 3.1	12.9 ± 3.1
Number of live offspring at birth		
Male	83	66
Female	73	55
Total	156	121
Mean ± S.D. per dam	14.2 ± 3.0	12.1 ± 4.7
Sex ratio ^{c)}		
Mean ± S.D. per dam	0.53 ± 0.09	0.55 ± 0.16 (9)
Number of dead offspring		
Total	2	8
Mean ± S.D. per dam	0.2 ± 0.4	0.8 ± 1.9
Delivery index (offspring) ^{d)}		
Mean% ± S.D. per dam	94.8 ± 4.7	86.9 ± 18.7
Birth index ^{e)}		
Mean% ± S.D. per dam	93.7 ± 5.4	81.7 ± 29.5
Live birth index ^{f)}		
Mean% ± S.D. per dam	98.9 ± 2.5	88.5 ± 31.3
Number of offspring on day 4		
Male	82	64
Female	71	54
Sex ratio ^{c)}		
Mean ± S.D. per dam	0.53 ± 0.09	0.55 ± 0.16 (9)
Viability index ^{g)}		
Mean% ± S.D. per dam	98.2 ± 3.1	97.5 ± 5.4 (9)
Number of external abnormalities ^{h)}	0	0

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

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

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

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

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

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

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

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

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

Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 38. Body weights of offspring (F₁) before weaning

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Number of dams	11	9
Male		
Days after birth		
0	6.4 ± 0.5	5.9 ± 0.7
4	10.5 ± 1.7	9.4 ± 1.8
Female		
Days after birth		
0	6.2 ± 0.5	5.6 ± 0.6 *
4	10.0 ± 1.5	9.1 ± 1.6

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

Figures in parentheses indicate number of dams.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Group	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
Control (vehicle: corn oil)	Number of offspring	156	156	155	153	153
	General appearance, No abnormality	156	155	153	153	153
	General appearance, Death		1	2		
4-IBA 30 mg/kg	Number of offspring	121	121	118	118	118
	General appearance, No abnormality	121	118	118	118	118
	General appearance, Death		3			
	Number of offspring					

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Table 40. Morphological observations of offspring (F₁)

Group	Control (vehicle: corn oil)	4-IBA 30 mg/kg
Dead pups		
Number of dead pups ^{a)}	5	11
Number of missing pups	3	6
Number of dead pups examined	2	5
Number of dead pups with external changes	0	0
Number of dead pups with visceral changes	0	0
Live pups		
Number of live pups examined (postnatal day 0)	156	121
Number of live pups with external changes	0	0
.....		
Number of live pups examined (postnatal day 4)	153	118
Number of live pups with external changes	0	0
Number of live pups with visceral changes	0	0

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

^{a)} including missing pups

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

[illegible]

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 30 mg/kg		Days of administration																																																								
Male No.		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25								
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post									
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of males	-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		
-	-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 30 mg/kg

Male No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b	a	a	a	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	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		
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Male No.		4-IBA 300/150 mg/kg																																															
		Days of administration																																															
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24	
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
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	Days of administration																																			
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	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		
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	9	6	6
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	9	6	6
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

b: Consciousness, Attitude, Sedation.

c: Mouth, Perioral smudge.

d: Anorectal region, Soiled perineal region.

e: Skin, Erosion.

f: General appearance, Exhaustion.

g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 30 mg/kg

Female No.	Days of administration																																			
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	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
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	7	7	
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	8	7	7	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

b: Consciousness, Attitude, Sedation.

c: Mouth, Perioral smudge.

d: Anorectal region, Soiled perineal region.

e: Skin, Erosion.

f: General appearance, Exhaustion.

g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Female No.	Days of administration																																					
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18			
	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		
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	5	5
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	8	5	5	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

b: Consciousness, Attitude, Sedation.

c: Mouth, Perioral smudge.

d: Anorectal region, Soiled perineal region.

e: Skin, Erosion.

f: General appearance, Exhaustion.

g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Days of administration																																			
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18	
	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
F04037	-	-	-	-	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	e	e	-	-	-	-	-	
F04039	-	-	-	-	-	a,b	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	f	g	-	-	
F04042	-	-	-	-	-	-	-	a,b	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	a,c,d	a,c,d	g	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04047	-	-	-	-	-	a,b	-	a,b	-	a,b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	a	-	a,b	-	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	7	7	3	0	0
-	12	12	12	12	12	7	12	7	12	9	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	10	10	6	6	3	0	0
a	0	0	0	0	0	5	0	5	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	4	0	4	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
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

b: Consciousness, Attitude, Sedation.

c: Mouth, Perioral smudge.

d: Anorectal region, Soiled perineal region.

e: Skin, Erosion.

f: General appearance, Exhaustion.

g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

[illegible]

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
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	5	
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

[illegible]

Pre: Before administration, Post: after administration.

(Continued)

+: General appearance, No abnormality.

a: General appearance, Emaciation.

b: Excretion. Decrease in amount of feces.

c: Behavior. Decrease in locomotor activity.

d: Fur Hair Coat, Bilorection.

d: Fur, Hair, Coat, Piloerection.

e. Anorectal region, Soiled period

f. Posture, Body position, Crouching

g: Excretion, Reddish urine.

h: Consciousness, Attitude, S

i: General appearance, Death.

j: General appearance, Moribund

k: Fur, Hair, Coat, Soiled fur

1: Behavior, Abnormal gait.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
F06060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	a	a	a	a	a	a	a	
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3		
-	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	5	5	3	
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
-	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

[illegible]

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Dam No.		Days of pregnancy					
		25		26		27	
		Pre	Post	Pre	Post	Pre	Post
F01001	#	-	-	-	-	-	-
Number of dams		1	1	1	1	1	
-		1	1	1	1	1	

Pre: Before administration, Post: after administration.

#: Non-pregnant

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

4-IBA 30 mg/kg

[illegible]

Pre: Before administration, Post: after administration.

#: Non-pregnant

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: General appearance. Emaciation.

c: Behavior. Abnormal gait.

d: Fur, Hair, Coat, Piloerection.

e: Posture, Body position, Crouching position.

f: Skin, Erosion.

g Nose, Smudge of perinasal area.

h: Anorectal region, Soiled perineal region.

i: Body temperature; Hypothermia.

j: General appearance, Death.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 30 mg/kg

Dam No.		Days of pregnancy					
		25		26		27	
		Pre	Post	Pre	Post	Pre	Post
F02018	#	-	-	-	-	-	-
F02019	#	-	-	-	-	-	-
Number of dams		2	2	2	2	2	2
-		2	2	2	2	2	2

Pre: Before administration, Post: after administration.

#: Non-pregnant

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

[illegible]

Pre: Before administration, Post: after administration.

#: Non-pregnant

∴ General appearance. No abnormality.

a: Excretion. Decrease in amount of feces.

b: General appearance, Emaciation.

c: Behavior. Abnormal gait.

d: Fur, Hair, Coat, Pilorection.

e: Posture, Body position, Crouching position.

f. Skin, Erosion.

g Nose, Smudge of perinasal area.

h: Anorectal region, Soiled perineal region.

i: Body temperature, Hypothermia.

j: General appearance, Death.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Dam No.	Days of pregnancy					
	25		26		27	
	Pre	Post	Pre	Post	Pre	Post
F03025	#	-	-	-	-	-
F03026	#	-	-	-	-	-
F03027	#	-	-	-	-	-
F03028	#	-	-	-	-	-
F03029	#	-	-	-	-	-
F03030	#	-	-	-	-	-
F03031	#	-	-	-	-	-
F03032	#	-	-	-	-	-
F03033	#	-	-	-	-	-
F03034	#	-	-	-	-	-
F03035	#	-	-	-	-	-
F03036	#	-	-	-	-	-
Number of dams	12	12	12	12	12	12
-	12	12	12	12	12	12

Pre: Before administration, Post: after administration.

#: Non-pregnant

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

4-IBA 300/150 mg/kg

Female No.	Days of pregnancy																																																						
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24						
	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							
F04037	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F04038	#	f	f	f	f	f	f	f	f	f	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-					
F04039	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F04040	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
F04043	#	-	-	-	-	a,b,c,d	a,b,c,d	a,b,c,d	a,b,c,d	a,b,c,d	a,b,c,d	a,b,c,d	a,b,c,d,e	a,b,c,d,e	a,b,c,d,e,h	a,b,c,d,e,h	j	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04044	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04045	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04046	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
F04047	#	-	-	b	b	b	b	b	b	b	b	b	b	b	-	-	-	-	-	-	-	-	-	b,c,d,e	b,c,d,e,g,i,j	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
-	9	9	8	8	7	7	7	7	7	7	8	8	8	8	9	9	9	9	8	8	9	9	8	8	8	8	8	8	8	8	7	7	7	7	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
a	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
b	0	0	1	1	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
c	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
d	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
e	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
f	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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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			
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	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			
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	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.

#: Non-pregnant

-: General appearance, No abnormality.

a: Excretion, Decrease in amount of feces.

b: General appearance, Emaciation.

c: Behavior, Abnormal gait.

d: Fur, Hair, Coat, Pilorection.

e: Posture, Body position, Crouching position.

f: Skin, Erosion.

g: Nose, Smudge of perinasal area.

h: Anorectal region, Soiled perineal region.

i: Body temperature, Hypothermia.

j: General appearance, Death.

(Continued)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 3-4(continued). General conditions in dams during pregnancy

4-IBA 300/150 mg/kg

Dam No.		Days of pregnancy					
		25		26		27	
		Pre	Post	Pre	Post	Pre	Post
F04037	#	-	-	-	-	-	-
F04038	#	-	-	-	-	-	-
F04039	#	-	-	-	-	-	-
F04040	#	-	-	-	-	-	-
F04044	#	-	-	-	-	-	-
F04045	#	-	-	-	-	-	-
F04047	#	-	-	-	-	-	-
F04048	#	-	-	-	-	-	-
Number of dams		8	8	8	8	8	8
-		8	8	8	8	8	8

Pre: Before administration, Post: after administration.

#: Non-pregnant

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation											
	0		1		2		3		4		5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01002	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-	-
F01007	-	-	-	-	-	-	-	-	-	-	-	-
F01008	#	#	-	-	-	-	-	-	-	-	-	-
F01009	#	#	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-
F01011	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	9	9	11	11	11	11	11	11	11	11	11	11
-	9	9	11	11	11	11	11	11	11	11	11	11

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

4-IBA 30 mg/kg

Dam No.	Days of lactation											
	0		1		2		3		4		5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-	-
F02015	#	#	-	-	-	-	-	-	-	-	-	-
F02016	#	#	-	-	-	-	-	-	-	-	-	-
F02017	-	a)										
F02020	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-
F02023	#	#	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	7	6	9	9	9	9	9	9	9	9	9	9
-	7	6	9	9	9	9	9	9	9	9	9	9

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a): Total litter loss on the lactation day 0

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 5-1. Detailed clinical observations of male rats

Control (vehicle: corn oil)

Male No.	Open-field observations ^{c)}																			
	Urination										Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
M01001	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01002	2	1	1	0	1	1	0				2	0	1	1	2	0	1			
M01003	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01004	0	0	0	0	0	0	0				0	0	0	1	0	0	0			
M01005	0	0	0	1	0	0	0				1	0	0	1	0	0	0			
M01006	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01007	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M01008	1	0	0	0	0	0	0	0	0		2	1	0	0	0	0	0	0	0	
M01009	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M01010	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M01011	0	0	0	0	1	0	0	0	0		0	0	0	0	0	0	0	0	0	
M01012	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
Total	3	1	1	1	2	1	0	0	0		5	1	1	3	2	0	1	0	0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 5-2. Detailed clinical observations of male rats

4-IBA (30 mg/kg)

Male No.	Open-field observations ^{c)}													
	Urination							Defecation						
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	0	0	0	0	0	1	0	0	0	0	0	0	0	0
M02014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02015	1	1	0	0	0	0	0	1	2	0	0	0	0	0
M02016	0	0	0	0	0	0	0	1	0	0	0	0	0	0
M02017	0	0	0	0	0	0	1	0	0	0	0	0	0	0
M02018	0	0	0	0	0	0	0	0	0	0	1	0	0	0
M02019	1	0	0	0	0	0	0	0	0	0	0	0	0	0
M02020	1	1	1	1	1	1	0	0	1	2	1	0	1	2
M02021	0	0	0	0	0	0	0	0	0	0	0	0	2	0
M02022	0	0	0	1	1	1	1	0	0	0	0	0	0	0
M02023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3	2	1	2	2	3	2	2	3	2	2	0	3	2
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 5-3. Detailed clinical observations of male rats

4-IBA (100 mg/kg)

Male No.	Open-field observations ^{c)}																			
	Urination										Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
M03025	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M03026	0	0	0	0	0	0	0				2	0	0	0	0	0	0			
M03027	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M03028	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M03029	1	0	0	0	1	0	0				0	0	0	0	0	0	0			
M03030	0	0	1	0	0	0	0				0	0	0	0	0	0	0			
M03031	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M03032	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M03033	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M03034	0	0	0	0	1	1	0	1	0		0	0	1	0	1	0	1	0	2	
M03035	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M03036	0	0	0	0	0	0	0	2	1		0	0	0	1	0	0	0	0	0	
Total score	1	0	1	0	2	1	0	3	1		2	0	1	1	1	0	1	0	2	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 5-4. Detailed clinical observations of male rats

4-IBA (300/150 mg/kg)

Male No.	Open-field observations ^{c)}																			
	Urination										Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
M04037	0	1	1	1	1	2	0				0	0	0	0	0	0	0			
M04038	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04039	0	0	0	0	0	0	0				0	0	0	1	0	0	0			
M04040	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04041	0	1	0	0	0	0	0				1	0	0	0	0	0	0			
M04042	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04043	0	0	0	0	0	0	0				0	0	0	0	0	0	0			
M04044	0	0	0	1	0	0	0	2	1		0	0	0	0	0	0	0	0	0	
M04045	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M04046	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M04047	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
M04048	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
Total score	0	2	1	2	1	2	0	2	1		1	0	0	1	0	0	0	0	0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 6-1-1. Detailed clinical observations of female rats

Control (vehicle: corn oil)

Female No.	Open-field observations ^{c)}																				
	Straub tail							Urination							Defecation						
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L
F01001	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01002	2	2	2	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
F01003	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01004	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01005	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01006	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01007	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01008	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01009	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01010	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01011	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F01012	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 6-1-2. Detailed clinical observations of female rats

4-IBA (30 mg/kg)

Female No.	Open-field observations ^{c)}																							
	Straub tail							Urination							Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L			
F02013	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02014	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02015	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02016	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02017	2	2	2	2	2	2		Total litter loss.	0	0	0	0	0	0		Total litter loss.	0	0	0	0	0	0	Total litter loss.	
F02018	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02019	2	2	2	2	3	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02020	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02021	2	2	2	2	2	2	2		0	1	0	0	0	0	0		0	0	0	0	0	0	0	
F02022	2	2	2	2	2	2	2		0	0	0	0	0	0	1		0	0	0	0	0	0	0	
F02023	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F02024	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	3:0	3:0	3:0	3:0	3:1	3:0	3:0		0	1	0	0	0	0	1		0	0	0	0	0	0	0	
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(11)		(12)	(12)	(12)	(12)	(12)	(12)	(11)		(12)	(12)	(12)	(12)	(12)	(12)	(11)	

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 6-1-3. Detailed clinical observations of female rats

4-IBA (100 mg/kg)

Female No.	Open-field observations ^{c)}																							
	Straub tail							Urination							Defecation									
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c	Pre	T8	T15	T24	T30	T36	L	Pre	T8	T15	T24	T30	T36	L			
F03025	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03026	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03027	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03028	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03029	2	2	2	2	2	2	2	1	1	1	1	0	1	0	0	0	0	0	1	0	0			
F03030	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03031	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03032	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03033	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03034	2	2	2	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0			
F03035	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0			
F03036	2	2	2	2	2	2	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0			
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	2	3	1	1	0	1	0	0	0	0	0	0	1	0			
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)			

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 6-1-4. Detailed clinical observations of female rats

4-IBA (300/150 mg/kg)

Female No.	Open-field observations ^{c)}																							
	Straub tail								Urination								Defecation							
	Pre ^a	T8 ^b	T15	T24	T30	T36	L ^c		Pre	T8	T15	T24	T30	T36	L		Pre	T8	T15	T24	T30	T36	L	
F04037	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04038	2	2	2	2	2	2	2		0	0	0	0	0	0	1		0	0	0	0	0	0	0	
F04039	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04040	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04041	2	2	2					Died	0	0	0					Died	0	0	0					Died
F04042	2	2						Died	0	0						Died	0	0						Died
F04043	2	2	2	2	2			Died	0	0	0	0	0			Died	0	0	0	0	0			Died
F04044	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04045	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
F04046	2	2	2	2	2			Died	0	0	0	0	0			Died	0	0	0	0	0			Died
F04047	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	2	0	0	
F04048	2	2	2	2	2	2	2		0	0	0	0	0	0	0		0	0	0	0	0	0	0	
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0		0	0	0	0	0	0	1		0	0	0	0	2	0	0	
(N)	(12)	(12)	(11)	(10)	(10)	(8)	(8)		(12)	(12)	(11)	(10)	(10)	(8)	(8)		(12)	(12)	(11)	(10)	(10)	(8)	(8)	

^a pre-treatment; ^b day 8 of treatment; ^c lactation period

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 6-2-1. Detailed clinical observations of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Open-field observations ^{c)}										Open-field observations										Defecation									
	Straub tail										Urination																			
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7 ^c	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14			
F05049	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F05050	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F05051	2	2	2	2	2	2	2			1	0	1	0	0	0	1			0	0	0	0	0	0	0					
F05052	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F05053	2	2	2	2	2	2	2			0	0	0	0	0	0	0			0	0	0	0	0	0	0					
F05054	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F05055	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F05056	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F05057	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
F05058	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0			
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)			

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomotor activity in home-cage, vocalization, tremor, convulsion), b)

Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA (300/150 mg/kg)

Female No.	Open-field observations ^{c)}										Open-field observations										Defecation									
	Straub tail										Urination																			
	Pre ^a	T8 ^b	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7 ^c	R14		Pre	T8	T15	T24	T30	T36	T42	R7	R14	
F06059	2	2	2							Died	0	0	0							Died	0	0	0							Died
F06060	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F06061	2	2	2	2	2	2	2				0	0	1	0	0	0	0				0	0	0	0	0	0	0			
F06062	2	2	2	2	2	2	2				0	0	0	0	0	0	0				0	0	0	0	0	0	0			
F06063	2	2	2							Died	0	0	0							Died	0	0	0							Died
F06064	2									Died	0									Died	0									Died
F06065	2	2	2	2	2	2	2	2	2		0	0	0	0	0	1	0	0	0		0	0	0	0	0	0	0	0	0	
F06066	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
F06067	2	2	2	2	2	2	2	2	2		0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
F06068	2	2	2							Died	0	0	0							Died	0	0	0							Died
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0		0	0	1	0	0	1	0	0	0		0	0	0	0	0	0	0	0	0	
(N)	(10)	(9)	(9)	(6)	(6)	(6)	(6)	(3)	(3)		(10)	(9)	(9)	(6)	(6)	(6)	(6)	(3)	(3)		(10)	(9)	(9)	(6)	(6)	(6)	(6)	(3)	(3)	

^a pre-treatment; ^b day 8 of treatment; ^c day 7 of recovery

Straub tail [2, not observed; 3, tail elevation]

Urination [frequency/30sec]

Defecation [frequency/30sec]

Except the above findings, there were no changes in all animals; a) Cage-side observation (posture in home-cage, locomotor activity in home-cage, vocalization, tremor, convulsion), b)

Observations made while handling (behavior while removing from cage, handling behavior, heart beats, body temperature, fur, skin/mucous membranes color, lacrimation, exophthalmos, pupillary size, salivation), and c) Open-field observations (posture, exploration, piloerection, palpebral opening, tremor, convulsion, respiratory rate, gait, stereotypy, bizarre behavior, straub tail, grooming, vocalization, touch response, withdrawal reflex, pinna reflex).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-1-1. Body weights of male rats

Control (vehicle: corn oil)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	347.5	356.8	368.2	387.3	402.9	422.0	439.0	449.9
M01002	391.2	408.9	419.1	450.9	460.7	488.0	507.4	520.4
M01003	376.6	381.7	394.7	414.4	433.3	450.3	472.5	490.3
M01004	396.5	408.7	426.1	452.6	475.1	496.8	519.5	533.3
M01005	377.0	387.3	402.7	422.1	445.2	470.7	498.3	510.2
M01006	367.7	384.8	395.0	418.2	436.3	458.0	474.3	498.7
M01007	362.2	372.4	382.1	402.1	419.0	437.3	452.4	471.7
M01008	390.4	396.5	408.3	432.3	447.0	471.2	492.5	508.8
M01009	394.1	405.0	419.2	444.5	461.2	490.7	521.1	536.5
M01010	404.8	417.5	431.5	464.9	489.6	521.8	554.4	586.1
M01011	398.4	416.3	429.6	449.3	474.3	493.1	516.0	532.3
M01012	365.5	382.3	393.4	427.9	442.6	465.2	491.0	511.9
Number of males	12	12	12	12	12	12	12	12
Mean	381.0	393.2	405.8	430.5	448.9	472.1	494.9	512.5
S.D.	17.6	18.8	20.0	23.0	24.8	27.9	32.1	34.6

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-1-2. Body weights of male rats

4-IBA 30 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	382.9	398.3	412.3	434.7	443.7	459.2	476.6	493.5
M02014	364.1	372.7	379.9	398.4	413.5	429.6	447.1	454.4
M02015	359.6	371.2	378.6	395.1	419.1	442.2	459.8	467.9
M02016	391.1	400.6	410.8	439.9	463.4	494.6	462.8	499.2
M02017	411.1	426.7	445.8	473.7	497.2	518.4	535.7	532.8
M02018	382.4	398.8	413.8	442.1	465.1	479.9	507.3	530.3
M02019	381.3	386.6	393.0	418.4	436.9	453.5	475.3	493.1
M02020	356.7	359.9	361.8	374.8	386.6	399.4	413.0	425.3
M02021	384.7	392.1	398.4	407.1	425.4	446.6	465.6	478.5
M02022	378.2	384.4	397.5	430.2	451.9	482.3	495.4	508.5
M02023	371.1	382.3	396.5	415.5	435.9	463.2	483.2	502.0
M02024	402.6	417.7	431.1	456.9	480.2	510.1	525.5	542.3
Number of males	12	12	12	12	12	12	12	12
Mean	380.5	390.9	401.6	423.9	443.2	464.9	478.9	494.0
S.D.	16.3	19.1	23.1	27.9	30.6	34.2	33.9	33.9
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	DU	DU

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-1-3. Body weights of male rats

4-IBA 100 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	386.4	395.8	414.5	440.2	441.0	461.3	476.5	490.2
M03026	347.8	344.2	351.6	368.7	392.4	413.2	433.4	442.1
M03027	373.4	383.5	389.6	398.4	427.9	451.8	474.7	495.0
M03028	396.6	402.8	422.2	448.5	465.8	486.8	509.9	514.8
M03029	401.7	416.4	438.3	479.5	499.3	517.2	531.3	528.1
M03030	392.0	407.3	420.2	452.9	478.4	507.2	531.8	546.7
M03031	390.1	380.1	389.8	424.5	429.4	436.1	449.7	458.4
M03032	379.2	379.5	395.6	413.4	430.5	444.8	451.1	463.1
M03033	366.5	373.5	378.2	390.4	404.0	408.6	433.4	444.8
M03034	354.7	359.3	361.0	374.0	388.6	409.8	424.6	438.1
M03035	391.9	412.2	423.3	449.6	468.9	480.3	499.9	521.5
M03036	371.1	378.5	387.3	400.3	427.3	441.6	466.6	484.7
Number of males	12	12	12	12	12	12	12	12
Mean	379.3	386.1	397.6	420.0	437.8	454.9	473.6	485.6
S.D.	16.9	21.7	26.6	34.7	34.6	36.8	37.5	36.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	DU	DU

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-1-4. Body weights of male rats

4-IBA 300/150 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	371.6	372.2	387.8	398.5	412.1	431.0	442.5	450.2
M04038	391.4	403.8	410.4	401.8	439.5	474.4	498.0	519.2
M04039	388.9	385.8	395.9	412.3	426.0	459.6	484.3	480.6
M04040	385.5	374.4	376.0	397.0	402.3	429.8	444.5	454.4
M04041	390.0	382.6	395.3	397.3	411.8	436.2	456.4	463.5
M04042	400.5	384.4	394.7	413.8	421.8	457.7	476.8	484.6
M04043	368.6	367.0	372.1	379.6	395.7	404.8	421.1	434.4
M04044	383.6	374.3	389.6	416.4	428.0	452.3	458.4	468.5
M04045	344.6	344.0	355.2	371.3	383.6	395.4	409.8	422.7
M04046	363.5	370.1	379.7	404.2	430.9	465.8	487.0	512.0
M04047	364.6	345.1	365.3	369.3	382.9	419.9	438.1	449.8
M04048	391.2	393.3	399.8	423.0	431.8	449.1	450.0	458.0
Number of males	12	12	12	12	12	12	12	12
Mean	378.7	374.8	385.2	398.7	413.9	439.7	455.6	466.5
S.D.	16.1	17.5	15.9	17.4	19.1	24.5	26.9	28.8
Significance	NS	NS	NS	*	**	NS	*	**
Statistical method	AN	AN	AN	DU	DU	AN	DU	DU

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-2-1. Body weights of male rats at the recovery period

Control (vehicle: corn oil)

Male No.	Days of recovery		
	1	7	14
M01008	504.4	509.5	512.7
M01009	540.5	552.3	551.5
M01010	584.3	600.9	618.3
M01011	527.9	543.2	546.7
M01012	515.8	527.1	534.6
Number of males	5	5	5
Mean	534.6	546.6	552.8
S.D.	30.9	34.5	39.6

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Days of recovery		
	1	7	14
M03032	458.7	455.6	460.5
M03033	447.7	469.2	482.4
M03034	435.5	444.3	455.4
M03035	515.8	533.2	539.5
M03036	478.4	501.4	515.8
Number of males	5	5	5
Mean	467.2	480.7	490.7
S.D.	31.4	36.3	36.2
Significance	**	*	*
Statistical method	DU	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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 7-2-3. Body weights of male rats at the recovery period

4-IBA 300/150 mg/kg

Male No.	Days of recovery		
	1	7	14
M04044	464.5	492.3	512.8
M04045	424.8	435.8	449.1
M04046	497.3	506.5	523.1
M04047	431.7	459.5	475.4
M04048	442.0	474.7	488.3
Number of males	5	5	5
Mean	452.1	473.8	489.7
S.D.	29.4	27.7	29.6
Significance	**	**	*
Statistical method	DU	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.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-1-1. Body weights of female rats

Control (vehicle: corn oil)

Female No.	Days of administration			
	1	4	7	14
F01001	228.4	235.1	238.9	245.2
F01002	235.8	236.1	235.6	248.2
F01003	248.2	255.7	263.1	266.3
F01004	263.3	268.8	268.1	274.3
F01005	228.6	229.7	227.9	239.1
F01006	255.8	255.2	258.0	268.9
F01007	233.6	246.7	256.2	267.4
F01008	270.6	274.9	273.5	300.4
F01009	263.0	266.0	277.3	278.3
F01010	233.3	239.1	237.9	251.1
F01011	239.6	235.3	245.5	258.1
F01012	247.8	256.5	261.5	267.2
Number of females	12	12	12	12
Mean	245.7	249.9	253.6	263.7
S.D.	14.7	15.1	16.1	16.8

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-1-2. Body weights of female rats

4-IBA 30 mg/kg

Female No.	Days of administration			
	1	4	7	14
F02013	255.9	266.5	270.8	287.0
F02014	256.1	257.4	254.9	272.4
F02015	246.8	246.4	259.5	267.0
F02016	233.8	232.0	238.8	241.6
F02017	254.0	258.8	260.0	261.2
F02018	244.7	252.4	244.8	261.3
F02019	252.7	254.9	255.3	264.6
F02020	235.9	238.0	237.1	254.0
F02021	224.6	231.8	233.1	243.4
F02022	233.5	226.3	235.0	233.9
F02023	232.6	237.7	247.2	268.5
F02024	257.4	262.0	267.4	275.6
Number of females	12	12	12	12
Mean	244.0	247.0	250.3	260.9
S.D.	11.4	13.5	12.8	15.4
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-1-3. Body weights of female rats

4-IBA 100 mg/kg

Female No.	Days of administration			
	1	4	7	14
F03025	261.7	260.8	263.3	266.4
F03026	249.8	255.6	251.8	254.3
F03027	232.7	235.7	237.3	248.4
F03028	269.3	255.1	277.7	283.8
F03029	242.9	244.1	251.1	255.3
F03030	263.0	272.6	277.4	289.2
F03031	235.3	235.1	240.2	250.9
F03032	222.5	244.0	243.5	246.4
F03033	245.6	245.5	238.1	255.8
F03034	229.7	224.1	235.6	247.8
F03035	253.0	259.9	261.3	269.2
F03036	250.3	247.6	244.2	260.4
Number of females	12	12	12	12
Mean	246.3	248.3	251.8	260.7
S.D.	14.4	13.3	15.0	14.0
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-1-4. Body weights of female rats

4-IBA 300/150 mg/kg

Female No.	Days of administration			
	1	4	7	14
F04037	231.3	211.1	240.4	252.1
F04038	226.7	220.8	224.5	233.8
F04039	253.7	235.9	244.6	236.4
F04040	257.6	251.5	261.2	266.4
F04041	220.7	232.7	230.0	231.4
F04042	232.6	223.7	234.6	
F04043	260.1	259.9	266.4	280.3
F04044	260.7	266.2	263.9	293.0
F04045	243.0	252.8	269.5	275.2
F04046	252.8	245.5	241.1	264.7
F04047	228.5	192.3	205.3	213.9
F04048	241.1	217.8	241.7	264.8
Number of females	12	12	12	11
Mean	242.4	234.2	243.6	255.6
S.D.	14.3	22.0	19.1	24.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-2-1. Body weights of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	221.7	232.5	236.6	241.3	255.3	258.8	265.0	265.8
F05050	276.7	278.5	290.9	313.0	338.3	331.4	336.5	338.0
F05051	244.9	250.5	261.4	272.6	275.6	289.8	297.9	303.0
F05052	262.9	266.8	273.9	290.3	311.4	321.6	335.1	335.7
F05053	244.6	249.2	246.4	263.3	273.0	272.9	288.5	298.3
F05054	251.4	253.9	256.6	282.2	300.2	328.1	333.5	357.1
F05055	251.2	255.5	259.1	279.3	292.5	302.4	300.9	304.1
F05056	243.8	251.6	260.7	265.9	288.1	291.2	294.4	294.1
F05057	264.1	268.5	280.8	294.0	310.1	311.7	314.8	321.0
F05058	259.1	265.3	264.7	267.4	286.0	294.5	298.2	302.9
Number of females	10	10	10	10	10	10	10	10
Mean	252.0	257.2	263.1	276.9	293.1	300.2	306.5	312.0
S.D.	15.0	12.9	15.8	19.7	23.4	23.6	23.3	26.3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	268.4	237.2	263.1	256.1				
F06060	235.3	254.8	246.6	247.8	265.0	279.7	283.4	271.0
F06061	262.3	264.2	261.6	270.2	301.9	308.2	307.6	325.3
F06062	245.7	243.9	245.7	270.5	278.4	288.1	288.5	295.8
F06063	250.8	233.6	248.7	255.1	191.8			
F06064	233.5	205.3	174.6					
F06065	250.0	237.5	258.0	258.2	279.7	270.3	279.4	279.1
F06066	226.0	210.6	209.5	226.0	234.5	245.9	237.1	213.8
F06067	230.7	242.4	235.0	268.6	275.5	272.6	292.6	296.8
F06068	252.1	229.5	193.0	221.9				
Number of females	10	10	10	9	7	6	6	6
Mean	245.5	235.9	233.6	252.7	261.0	277.5	281.4	280.3
S.D.	13.9	17.9	30.7	18.1	36.6	20.7	23.8	37.5
Significance	NS	**	*	*	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-3-1. Body weights of female rats at the recovery period

Control (vehicle: corn oil)

Female No.	Days of recovery		
	1	7	14
F05054	355.6	357.5	375.2
F05055	305.1	312.4	313.2
F05056	303.3	310.3	296.6
F05057	320.4	327.2	328.4
F05058	309.4	314.4	316.4
Number of females	5	5	5
Mean	318.8	324.4	326.0
S.D.	21.6	19.7	29.8

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 8-3-2. Body weights of female rats at the recovery period

4-IBA 300/150 mg/kg

Female No.	Days of recovery		
	1	7	14
F06065	270.2	284.0	310.3
F06066	212.0	251.7	241.7
F06067	295.3	297.6	297.5
Number of females	3	3	3
Mean	259.2	277.8	283.2
S.D.	42.7	23.6	36.5
Significance	*	*	NS
Statistical method	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: corn oil)

Dam No.	Days of pregnancy				
	0	7	14	20	27
F01001	> 259.7	> 289.6	> 287.0	> 289.8	> 276.3
F01002	261.4	285.6	320.9	396.0	
F01003	272.8	305.4	340.0	420.9	
F01004	291.1	345.8	402.2	514.5	
F01005	241.9	273.3	305.2	391.4	
F01006	286.3	326.0	358.6	419.0	
F01007	274.6	312.7	350.1	439.0	
F01008	309.8	346.3	386.7	437.9	
F01009	294.4	320.4	365.8	439.4	
F01010	267.8	298.7	330.0	409.0	
F01011	261.1	294.3	325.2	406.7	
F01012	282.4	316.7	358.9	440.9	
Number of dams	11	11	11	11	
Mean	276.7	311.4	349.4	428.6	
S.D.	18.8	23.1	29.1	33.6	

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

4-IBA 30 mg/kg

Dam No.	Days of pregnancy				
	0	7	14	20	27
F02013	303.9	338.2	369.8	435.7	
F02014	286.9	325.4	358.3	445.6	
F02015	262.7	305.8	335.5	428.0	
F02016	253.5	276.6	309.6	360.2	
F02017	263.7	304.9	340.7	447.4	
F02018	> 272.3	> 295.4	> 302.1	> 311.5	> 289.1
F02019	> 262.7	> 274.1	> 284.9	> 278.3	> 271.0
F02020	257.3	287.3	321.3	392.0	
F02021	247.5	290.9	321.0	395.3	
F02022	237.8	259.6	305.3	376.7	
F02023	274.4	310.9	348.1	440.6	
F02024	273.8	304.2	336.9	420.8	
Number of dams	10	10	10	10	
Mean	266.2	300.4	334.7	414.2	
S.D.	19.4	22.9	20.7	31.0	
Significance	NS	NS	NS	NS	
Statistical method	TT	TT	TT	TT	

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation	
	0	4
F01002	287.2	309.9
F01003	315.0	331.9
F01004	407.4	399.1
F01005	267.9	305.7
F01006	365.7	362.9
F01007	313.1	337.2
F01008	359.4	369.0
F01009	338.1	336.5
F01010	295.7	324.6
F01011	311.8	332.9
F01012	323.3	345.0
Number of dams	11	11
Mean	325.9	341.3
S.D.	39.7	27.1

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

4-IBA 30 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	358.0	356.0
F02014	333.1	357.4
F02015	341.7	317.5
F02016	282.3	266.7
F02017	309.2	
F02020	309.0	305.2
F02021	331.8	321.9
F02022	298.2	276.3
F02023	348.8	338.3
F02024	311.1	316.4
Number of dams	10	9
Mean	322.3	317.3
S.D.	24.1	31.5
Significance	NS	NS
Statistical method	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-1-1. Food consumption of male rats

Control (vehicle: corn oil)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	24.3	23.5	22.1	19.2	18.2	23.9
M01002	28.4	24.7	22.1	22.5	20.7	20.3
M01003	21.3	23.4	21.5	24.5	23.3	23.7
M01004	28.6	27.7	24.6	25.4	27.1	26.1
M01005	26.0	21.1	20.8	24.0	22.2	25.2
M01006	24.5	26.9	16.5	19.0	23.3	22.1
M01007	26.6	22.5	15.5	22.2	21.3	24.1
M01008	25.8	21.9	23.3	26.0	22.1	21.5
M01009	27.6	25.8	26.3	27.5	26.6	27.6
M01010	26.9	28.5	23.0	28.7	26.0	29.6
M01011	28.8	29.1	22.5	24.7	21.9	25.5
M01012	28.6	26.8	22.2	26.9	27.2	28.0
Number of males	12	12	12	12	12	12
Mean	26.5	25.2	21.7	24.2	23.3	24.8
S.D.	2.3	2.7	3.0	3.1	2.8	2.8

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-1-2. Food consumption of male rats

4-IBA 30 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	25.4	19.6	20.1	20.6	19.2	24.9
M02014	21.7	22.0	20.8	21.2	20.6	22.9
M02015	24.4	22.2	20.7	20.6	20.5	17.7
M02016	25.9	23.7	23.1	26.1	18.3	25.3
M02017	25.6	30.1	22.3	23.5	20.1	21.2
M02018	28.2	21.7	22.5	22.8	22.1	21.6
M02019	27.1	23.3	23.0	20.9	22.1	23.0
M02020	21.4	20.9	16.7	21.1	19.6	20.0
M02021	27.2	24.4	24.6	25.2	25.7	25.2
M02022	21.7	23.6	18.7	24.0	23.0	23.9
M02023	25.7	23.2	20.5	25.3	22.8	24.7
M02024	27.3	24.9	23.3	23.3	23.8	23.3
Number of males	12	12	12	12	12	12
Mean	25.1	23.3	21.4	22.9	21.5	22.8
S.D.	2.4	2.6	2.2	2.0	2.1	2.3
Significance	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	KW	AN	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-1-3. Food consumption of male rats

4-IBA 100 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	27.0	24.6	22.6	23.1	24.9	25.6
M03026	17.6	21.4	18.1	25.1	19.0	23.3
M03027	21.9	17.9	18.8	25.0	21.7	25.4
M03028	22.6	23.0	20.6	25.4	22.6	23.0
M03029	25.5	25.5	24.0	20.8	20.3	28.6
M03030	21.6	29.6	21.7	25.7	22.4	26.6
M03031	23.1	23.6	21.1	23.2	19.7	19.6
M03032	20.3	23.6	22.0	22.0	21.8	20.9
M03033	22.4	22.4	24.9	21.7	19.9	24.4
M03034	23.7	24.2	21.4	23.6	21.1	22.5
M03035	23.3	25.2	19.0	23.0	22.0	23.1
M03036	22.0	21.4	21.8	22.9	24.8	26.2
Number of males	12	12	12	12	12	12
Mean	22.6	23.5	21.3	23.5	21.7	24.1
S.D.	2.4	2.8	2.0	1.6	1.9	2.5
Significance	*	NS	NS	NS	NS	NS
Statistical method	DT	AN	KW	AN	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-1-4. Food consumption of male rats

4-IBA 300/150 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	16.6	27.9	26.5	21.0	17.1	23.1
M04038	28.1	33.4	14.2	28.5	20.4	31.3
M04039	21.7	23.0	28.3	25.2	23.8	21.6
M04040	20.0	25.8	24.1	25.8	22.5	22.8
M04041	26.4	25.1	21.3	25.9	22.2	27.3
M04042	12.3	21.0	25.3	25.6	20.0	25.3
M04043	20.3	22.7	19.8	20.4	19.9	20.9
M04044	18.8	24.4	27.9	24.7	23.3	24.1
M04045	22.1	27.7	24.7	21.8	20.6	22.2
M04046	21.4	28.1	32.9	29.8	26.4	30.4
M04047	8.9	28.2	11.1	22.2	20.8	22.3
M04048	21.3	24.3	21.6	20.0	23.0	20.0
Number of males	12	12	12	12	12	12
Mean	19.8	26.0	23.1	24.2	21.7	24.3
S.D.	5.3	3.3	6.1	3.2	2.4	3.6
Significance	**	NS	NS	NS	NS	NS
Statistical method	DT	AN	KW	AN	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-2-1. Food consumption of male rats at the recovery period

Control (vehicle: corn oil)

Male No.	Days of recovery	
	6	12
M01008	24.4	24.8
M01009	30.3	30.3
M01010	29.3	29.7
M01011	28.3	30.9
M01012	32.6	31.7
Number of males	5	5
Mean	29.0	29.5
S.D.	3.0	2.7

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Days of recovery	
	6	12
M03032	23.4	24.4
M03033	32.9	34.9
M03034	24.3	27.8
M03035	26.4	24.5
M03036	30.0	28.1
Number of males	5	5
Mean	27.4	27.9
S.D.	4.0	4.3
Significance	NS	NS
Statistical method	AN	AN

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

NS: Not significantly different from the control group.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 11-2-3. Food consumption of male rats at the recovery period

4-IBA 300/150 mg/kg

Male No.	Days of recovery	
	6	12
M04044	24.8	29.7
M04045	25.5	27.8
M04046	26.8	29.5
M04047	24.3	28.4
M04048	24.7	26.3
Number of males	5	5
Mean	25.2	28.3
S.D.	1.0	1.4
Significance	NS	NS
Statistical method	AN	AN

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

NS: Not significantly different from the control group.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-1-1. Food consumption of female rats

Control (vehicle: corn oil)

Female No.	Days of administration		
	1	7	14
F01001	14.4	19.6	19.0
F01002	15.1	17.7	11.7
F01003	17.7	19.2	14.9
F01004	12.6	18.6	8.9
F01005	17.6	17.5	11.2
F01006	16.2	18.5	11.5
F01007	18.9	20.1	17.3
F01008	22.2	24.8	12.1
F01009	20.3	19.6	17.1
F01010	16.9	19.3	13.2
F01011	19.9	14.6	14.8
F01012	13.7	21.2	19.5
Number of females	12	12	12
Mean	17.1	19.2	14.3
S.D.	2.9	2.4	3.4

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-1-2. Food consumption of female rats

4-IBA 30 mg/kg

Female No.	Days of administration		
	1	7	14
F02013	19.4	19.8	10.4
F02014	19.0	18.2	13.0
F02015	19.9	13.5	15.5
F02016	17.4	13.5	12.3
F02017	13.9	20.2	13.3
F02018	15.8	17.2	11.7
F02019	16.9	19.3	15.7
F02020	17.0	22.1	12.0
F02021	13.7	17.7	11.4
F02022	16.3	14.3	14.8
F02023	17.6	18.7	18.9
F02024	19.0	20.0	15.2
Number of females	12	12	12
Mean	17.2	17.9	13.7
S.D.	2.0	2.8	2.4
Significance	NS	NS	NS
Statistical method	DU	AN	KW

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-1-3. Food consumption of female rats

4-IBA 100 mg/kg

Female No.	Days of administration		
	1	7	14
F03025	10.6	18.2	17.3
F03026	9.3	21.6	16.0
F03027	14.7	14.1	13.5
F03028	14.0	20.7	14.9
F03029	13.4	15.4	17.1
F03030	19.6	24.9	20.0
F03031	15.8	16.9	9.6
F03032	17.3	19.5	13.7
F03033	18.4	21.8	13.0
F03034	15.8	19.5	13.1
F03035	12.5	18.4	17.6
F03036	15.8	20.7	15.3
Number of females	12	12	12
Mean	14.8	19.3	15.1
S.D.	3.0	3.0	2.7
Significance	NS	NS	NS
Statistical method	DU	AN	KW

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-1-4. Food consumption of female rats

4-IBA 300/150 mg/kg

Female No.	Days of administration		
	1	7	14
F04037	11.6	20.4	20.8
F04038	10.9	13.4	13.9
F04039	13.8	16.4	14.6
F04040	13.8	14.7	14.8
F04041	12.0	20.4	0.0
F04042	11.3	18.6	
F04043	12.8	27.6	12.2
F04044	16.7	25.5	18.9
F04045	15.7	25.8	20.3
F04046	12.5	18.8	15.0
F04047	9.3	19.8	20.2
F04048	16.2	17.9	20.9
Number of females	12	12	11
Mean	13.1	19.9	15.6
S.D.	2.3	4.4	6.1
Significance	**	NS	NS
Statistical method	DU	AN	KW

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-2-1. Food consumption of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	18.0	20.2	17.1	15.4	15.0	18.1	14.3
F05050	21.8	21.6	21.6	23.7	21.5	13.2	19.2
F05051	16.5	15.9	15.9	18.1	16.8	16.6	15.3
F05052	16.2	18.1	15.9	16.6	23.0	13.6	18.0
F05053	15.2	19.7	13.3	23.5	19.9	16.0	18.9
F05054	11.7	21.2	17.3	22.4	16.5	16.8	20.3
F05055	15.0	20.5	14.3	19.8	16.5	14.7	15.6
F05056	15.0	22.1	17.8	12.6	11.8	19.0	16.8
F05057	16.6	17.8	15.8	16.8	18.7	18.3	13.5
F05058	14.6	23.7	19.3	14.6	13.8	23.0	17.9
Number of females	10	10	10	10	10	10	10
Mean	16.1	20.1	16.8	18.4	17.4	16.9	17.0
S.D.	2.6	2.3	2.4	3.9	3.5	2.9	2.3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	10.8	17.5	0.4				
F06060	13.1	23.3	29.2	20.2	18.4	18.7	21.8
F06061	14.0	24.4	10.2	20.5	18.1	15.2	19.3
F06062	14.0	22.4	13.2	20.8	22.0	19.4	18.6
F06063	14.3	15.4	15.9	0.5			
F06064	11.3						
F06065	10.0	16.8	23.6	20.5	18.8	19.4	18.3
F06066	10.4	18.0	12.5	15.3	10.6	15.6	9.8
F06067	13.8	22.9	18.8	21.5	21.3	16.3	17.0
F06068	11.4	0.8	15.0				
Number of females	10	9	9	7	6	6	6
Mean	12.3	17.9	15.4	17.0	18.2	17.4	17.5
S.D.	1.7	7.2	8.2	7.6	4.1	1.9	4.1
Significance	**	NS	NS	NS	NS	NS	NS
Statistical method	TT	AW	AW	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-3-1. Food consumption of female rats at the recovery period

Control (vehicle: corn oil)

Female No.	Days of recovery	
	6	12
F05054	16.7	19.2
F05055	19.2	14.8
F05056	21.5	22.8
F05057	21.8	23.0
F05058	23.7	19.6
Number of females	5	5
Mean	20.6	19.9
S.D.	2.7	3.3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 12-3-2. Food consumption of female rats at the recovery period

4-IBA 300/150 mg/kg

Female No.	Days of recovery	
	6	12
F06065	20.0	28.3
F06066	23.3	22.3
F06067	19.6	15.7
Number of females	3	3
Mean	21.0	22.1
S.D.	2.0	6.3
Significance	NS	NS
Statistical method	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: corn oil)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	> 17.2	> 21.4	> 17.0	> 14.6
F01002	19.3	20.3	22.7	14.8
F01003	16.0	17.6	20.6	15.6
F01004	24.1	30.0	34.3	27.4
F01005	23.7	19.5	21.7	6.7
F01006	24.4	22.3	24.0	20.3
F01007	18.0	24.4	24.6	15.2
F01008	26.4	28.9	24.5	21.8
F01009	20.4	26.9	30.2	19.3
F01010	22.0	23.8	20.1	14.9
F01011	18.6	18.6	22.4	19.6
F01012	18.6	25.2	25.2	17.0
Number of dams	11	11	11	11
Mean	21.0	23.4	24.6	17.5
S.D.	3.3	4.2	4.2	5.2

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

4-IBA 30 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	23.4	22.3	20.2	21.0
F02014	18.2	18.6	20.8	19.3
F02015	23.2	26.0	24.2	20.8
F02016	15.7	19.0	19.9	1.7
F02017	19.2	20.3	26.9	1.4
F02018	> 21.4	> 18.3	> 19.4	> 16.4
F02019	> 26.3	> 14.6	> 18.6	> 16.9
F02020	25.3	20.9	23.2	21.0
F02021	22.2	16.7	21.1	18.2
F02022	13.9	26.3	22.2	13.3
F02023	18.8	24.3	25.2	20.0
F02024	16.2	23.6	20.6	17.2
Number of dams	10	10	10	10
Mean	19.6	21.8	22.4	15.4
S.D.	3.8	3.2	2.4	7.7
Significance	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT

>: Excluded from analysis (not pregnant)

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: corn oil)

Dam No.	Days of lactation
	3
F01002	42.9
F01003	33.1
F01004	26.2
F01005	37.4
F01006	31.1
F01007	33.5
F01008	29.5
F01009	28.8
F01010	44.6
F01011	39.8
F01012	38.2
Number of dams	11
Mean	35.0
S.D.	6.0

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

4-IBA 30 mg/kg

Dam No.	Days of lactation
	3
F02013	34.0
F02014	38.7
F02015	26.8
F02016	20.2
F02020	29.7
F02021	36.5
F02022	30.4
F02023	28.6
F02024	29.7
Number of dams	9
Mean	30.5
S.D.	5.5
Significance	NS
Statistical method	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 15-1. Functional findings of male rats at the end of the dosing period

Control (vehicle: corn oil)

Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01002	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Appendix 15-2

Functional findings of male rats at the end of the dosing period

4-IBA (30 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M02013	2	2	2	2	+	+	+
M02014	2	2	2	2	+	+	+
M02015	2	2	2	2	+	+	+
M02016	2	2	2	2	+	+	+
M02017	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 15-3. Functional findings of male rats at the end of the dosing period

4-IBA (100 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M03025	2	2	2	2	+	+	+
M03026	2	2	2	2	+	+	+
M03027	2	2	2	2	+	+	+
M03028	2	2	2	2	+	+	+
M03029	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Appendix 15-4

Functional findings of male rats at the end of the dosing period

4-IBA (300/150 mg/kg)

Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	2	+	+	+
M04041	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 16-1. Functional findings of female rats at the end of the dosing period

Control (vehicle: corn oil)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01003	2	2	2	2	+	+	+
F01007	2	2	2	2	+	+	+
F01009	2	2	2	2	+	+	+
F01011	2	2	2	2	+	+	+
F01012	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Appendix 16-2

Functional findings of female rats at the end of the dosing period

4-IBA (30 mg/kg)

Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02015	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02022	2	2	2	2	+	+	+
F02023	2	2	2	2	+	+	+
F02024	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 16-3. Functional findings of female rats at the end of the dosing period ,satellite group

Control (vehicle: corn oil)

Female, satellite group

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F05049	2	2	2	2	+	+	+
F05050	2	2	2	2	+	+	+
F05051	2	2	2	2	+	+	+
F05052	2	2	2	2	+	+	+
F05053	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Appendix 16-4

Functional findings of female rats at the end of the dosing period

4-IBA (300/150 mg/kg)

Female, satellite group

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06060	2	2	2	2	+	+	+
F06061	2	2	2	2	+	+	+
F06062	2	2	2	2	+	+	+
F06065	2	2	2	2	+	+	+
F06066	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 17. Assessment of grip strength of male rats

Control (vehicle: corn oil)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M01001	1.016	0.289
M01002	0.978	0.441
M01003	0.745	0.435
M01004	1.131	0.784
M01005	0.877	0.674
Number of males	5	5
Mean	0.949	0.525
S.D.	0.146	0.200

4-IBA (30 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M02013	0.968	0.628
M02014	0.727	0.672
M02015	0.967	0.409
M02016	0.651	0.567
M02017	1.001	0.448
Number of males	5	5
Mean	0.863	0.545
S.D.	0.161	0.113

4-IBA (100 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M03025	0.988	0.641
M03026	1.086	0.338
M03027	0.940	0.484
M03028	0.877	0.527
M03029	0.812	0.429
Number of males	5	5
Mean	0.941	0.484
S.D.	0.105	0.113

4-IBA(300/150 mg/kg)

Male No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
M04037	1.079	0.671
M04038	0.781	0.422
M04039	0.954	0.542
M04040	1.037	0.560
M04041	1.170	0.623
Number of males	5	5
Mean	1.004	0.564
S.D.	0.147	0.094

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 18. Assessment of grip strength of female rats

Control (vehicle: cornoil)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F01003	1.016	0.755
F01007	1.037	0.462
F01009	0.804	0.593
F01011	0.843	0.472
F01012	1.175	0.578
Number of females	5	5
Mean	0.975	0.572
S.D.	0.152	0.118

4-IBA (30 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F02015	1.095	0.608
F02016	0.982	0.502
F02022	0.884	0.510
F02023	0.777	0.650
F02024	1.139	0.583
Number of females	5	5
Mean	0.975	0.571
S.D.	0.149	0.064

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: cornoil)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F05049	1.208	0.632
F05050	0.820	0.439
F05051	0.968	0.659
F05052	0.720	0.526
F05053	0.935	0.534
Number of females	5	5
Mean	0.930	0.558
S.D.	0.184	0.089

4-IBA (300/150 mg/kg)

Female No.	Administration period	
	Forelimb	Hindlimb
	(kg)	(kg)
F06060	1.131	0.594
F06061	0.912	0.633
F06062	0.852	0.454
F06065	1.045	0.721
F06066	0.895	0.554
Number of females	5	5
Mean	0.967	0.591
S.D.	0.117	0.099

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-1-1. Motor activity of male rats

Control (vehicle: corn oil)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1081	935	1017	714	3747	32	20	26	6	84
M01002	1006	407	403	3	1819	27	6	11	0	44
M01003	1168	832	799	652	3451	37	23	15	8	83
M01004	933	791	492	286	2502	27	29	27	2	85
M01005	1231	1105	895	887	4118	41	21	22	12	96
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1084	814	721	508	3127	33	20	20	6	78
S.D.	120	258	263	357	945	6	8	7	5	20

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-1-2. Motor activity of male rats

4-IBA (30 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	878	912	761	425	2976	26	34	24	3	87
M02014	1067	872	685	253	2877	20	27	17	10	74
M02015	1062	1024	654	703	3443	34	20	23	14	91
M02016	817	920	336	494	2567	21	27	5	9	62
M02017	1278	1064	507	599	3448	39	32	7	21	99
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1020	958	589	495	3062	28	28	15	11	83
S.D.	182	81	169	171	381	8	5	9	7	15

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-1-3. Motor activity of male rats

4-IBA (100 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	1009	863	821	532	3225	28	16	16	15	75
M03026	1051	918	619	226	2814	23	32	19	1	75
M03027	1245	1100	1151	482	3978	34	24	21	7	86
M03028	1110	1029	641	674	3454	39	31	14	16	100
M03029	1860	1651	1381	1590	6482	35	27	17	38	117
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1255	1112	923	701	3991	32	26	17	15	91
S.D.	350	315	333	523	1455	6	6	3	14	18

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-1-4. Motor activity of male rats

4-IBA (300/150 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	873	757	549	181	2360	26	16	5	1	48
M04038	1287	857	393	934	3471	51	15	6	17	89
M04039	1194	1019	192	77	2482	25	11	0	0	36
M04040	615	567	142	401	1725	28	14	3	13	58
M04041	1072	1101	445	742	3360	32	38	13	20	103
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1008	860	344	467	2680	32	19	5 **	10	67
S.D.	269	212	172	365	732	11	11	5	9	28

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-2-1. Motor activity of male rats, recovery period

Control (vehicle: corn oil)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01008	1191	1020	909	781	3901	35	28	16	19	98
M01009	1281	1035	1190	748	4254	50	39	38	20	147
M01010	1064	1068	923	855	3910	25	32	24	13	94
M01011	1295	1239	993	1117	4644	36	43	39	39	157
M01012	1379	1202	1186	1134	4901	51	33	28	16	128
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1242	1113	1040	927	4322	39	35	29	21	125
S.D.	120	101	139	185	445	11	6	10	10	28

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-2-2. Motor activity of male rats, recovery period

4-IBA (100 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03032	1021	963	676	594	3254	26	19	25	15	85
M03033	1238	1144	1138	807	4327	38	34	24	22	118
M03034	1194	1032	799	870	3895	53	31	15	20	119
M03035	1285	1182	1163	898	4528	47	28	23	17	115
M03036	1232	1167	1021	847	4267	39	42	38	24	143
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1194	1098	959	803	4054	41	31	25	20	116
S.D.	102	96	214	122	502	10	8	8	4	21

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 20-2-3. Motor activity of male rats, recovery period

4-IBA (300/150 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04044	1345	983	614	677	3619	43	28	10	16	97
M04045	1183	1102	969	753	4007	23	31	40	19	113
M04046	1229	1063	960	1094	4346	28	8	17	8	61
M04047	1176	917	726	730	3549	20	20	11	8	59
M04048	1665	1811	1785	1773	7034	33	24	34	15	106
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1320	1175	1011	1005	4511	29	22	22	13	87
S.D.	205	363	459	459	1446	9	9	14	5	25

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 21-1. Motor activity of female rats

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01003	872	820	342	44	2078	28	29	7	0	64
F01007	971	588	430	247	2236	21	13	8	0	42
F01009	1112	676	841	572	3201	30	9	22	11	72
F01011	1025	352	321	173	1871	17	2	0	0	19
F01012	1356	820	325	371	2872	37	19	3	12	71
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1067	651	452	281	2452	27	14	8	5	54
S.D.	183	194	222	201	562	8	10	8	6	23

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 21-2. Motor activity of female rats

4-IBA (30 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02015	810	341	339	61	1551	26	50	6	0	82
F02016	890	550	66	25	1531	17	11	0	0	28
F02022	968	659	615	511	2753	25	2	5	1	33
F02023	1240	750	442	362	2794	31	8	3	1	43
F02024	1055	630	669	366	2720	15	6	5	3	29
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	993	586	426	265	2270	23	15	4	1	43
S.D.	166	155	241	212	666	7	20	2	1	23

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 22-1. Motor activity of female rats, satellite group

Control (vehicle: corn oil)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1237	1004	1210	643	4094	39	18	25	8	90
F05050	1123	1053	915	679	3770	35	32	20	14	101
F05051	1253	1003	536	570	3362	27	15	8	5	55
F05052	1205	822	926	838	3791	28	8	20	18	74
F05053	1855	1521	1843	1453	6672	36	11	18	12	77
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1335	1081	1086	837	4338	33	17	18	11	79
S.D.	295	261	486	358	1331	5	9	6	5	17

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 22-2. Motor activity of female rats, satellite group

4-IBA (300/150 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06060	1165	736	467	33	2401	45	19	6	0	70
F06061	1347	1170	1027	878	4422	47	37	20	23	127
F06062	1350	919	973	393	3635	35	19	16	3	73
F06065	835	704	668	323	2530	41	21	34	10	106
F06066	1140	1156	627	634	3557	26	28	9	14	77
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1167	937	752	452	3309	39	25	17	10	91
S.D.	210	222	239	320	842	8	8	11	9	25

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: corn oil)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	8.5	+	-	-	-	-	±	-	-	-	±	-
M01002	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
M01003	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	-	-
M01004	Light yellow	+	6.5	2+	-	+	-	-	+	-	-	-	+	-
M01005	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01001	61.0	1.014	23.4	67.7	29.1	1.43	4.13	1.78
M01002	13.2	1.072	150.1	214.9	162.2	1.98	2.84	2.14
M01003	12.6	1.058	82.0	205.6	112.8	1.03	2.59	1.42
M01004	12.7	1.064	97.3	215.7	127.0	1.24	2.74	1.61
M01005	9.3	1.071	147.5	232.7	163.3	1.37	2.16	1.52
Number of males	5	5	5	5	5	5	5	5
Mean	21.8	1.056	100.1	187.3	118.9	1.41	2.89	1.69
±S.D.	22.0	0.024	52.4	67.6	54.8	0.35	0.74	0.28

Turbidity, -: negative; +: slight

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

4-IBA (30 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	6.5	2+	-	+	-	-	±	-	-	-	±	-
M02014	Yellow	-	6.5	2+	-	+	-	-	2+	-	-	-	±	-
M02015	Light yellow	+	6.5	+	-	+	-	-	+	-	-	-	±	-
M02016	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	±	-
M02017	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M02013	20.9	1.038	64.4	167.9	87.7	1.35	3.51	1.83
M02014	6.6	1.077	133.3	205.1	160.7	0.88	1.35	1.06
M02015	17.3	1.047	79.9	156.6	96.7	1.38	2.71	1.67
M02016	10.7	1.056	140.0	170.8	143.9	1.50	1.83	1.54
M02017	9.6	1.070	119.7	199.2	138.1	1.15	1.91	1.33
Number of males	5	5	5	5	5	5	5	5
Mean	13.0	1.058	107.5	179.9	125.4	1.25	2.26	1.49
±S.D.	5.9	0.016	33.5	21.1	31.6	0.24	0.85	0.30

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

Turbidity, -: negative; +: slight

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

4-IBA (100 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Light yellow	-	6.5	+	-	+	-	-	±	-	-	-	-	-
M03026	Light yellow	-	8.5	+	-	-	-	-	±	-	-	-	±	-
M03027	Light yellow	-	7.0	+	-	+	-	-	±	-	-	-	±	-
M03028	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
M03029	Light yellow	-	8.0	+	-	+	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03025	21.6	1.051	106.9	176.6	113.1	2.31	3.81	2.44
M03026	20.5	1.047	108.9	183.2	116.4	2.23	3.76	2.39
M03027	17.5	1.057	106.4	194.4	127.4	1.86	3.40	2.23
M03028	36.7	1.025	50.4	92.0	55.2	1.85	3.38	2.03
M03029	17.0	1.053	134.4	165.3	121.4	2.28	2.81	2.06
Number of males	5	5	5	5	5	5	5	5
Mean	22.7	1.047	101.4	162.3	106.7	2.11*	3.43	2.23
±S.D.	8.1	0.013	30.8	40.7	29.3	0.23	0.40	0.19

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

Turbidity, -: negative

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

4-IBA (300/150 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	6.5	±	-	+	-	-	±	-	-	-	-	-
M04038	Light yellow	-	6.5	+	-	±	-	2+	±	+	-	-	±	-
M04039	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-
M04040	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M04041	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04037	25.1	1.037	69.3	143.8	73.4	1.74	3.61	1.84
M04038	48.4	1.042	85.6	165.9	88.0	4.14	8.03	4.26
M04039	21.6	1.044	82.6	166.5	93.5	1.78	3.60	2.02
M04040	21.4	1.050	92.0	183.2	113.2	1.97	3.92	2.42
M04041	25.0	1.043	83.2	150.7	95.1	2.08	3.77	2.38
Number of males	5	5	5	5	5	5	5	5
Mean	28.3	1.043	82.5	162.0	92.6	2.34	4.59	2.58
±S.D.	11.4	0.005	8.3	15.4	14.3	1.01	1.93	0.97

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

Turbidity, -: negative

Protein, ±: $10 \leq$ and < 30 mg/dL; +: $30 \leq$ and < 100 mg/dL; 2+: $100 \leq$ and < 300 mg/dL

Glucose, -: negative

Ketone, -: negative; ±: $5 \leq$ and < 10 mg/dL; +: $10 \leq$ and < 40 mg/dL; 2+: $40 \leq$ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats of the recovery period

Control (vehicle: corn oil)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	+	8.0	2+	-	+	-	-	+	-	-	-	+	-
M01009	Light yellow	-	8.0	+	-	-	-	-	±	-	-	-	±	-
M01010	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M01011	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M01012	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01008	8.4	1.079	139.4	235.0	158.5	1.17	1.97	1.33
M01009	33.7	1.028	43.9	123.0	63.4	1.48	4.15	2.14
M01010	16.3	1.070	107.7	202.6	134.0	1.76	3.30	2.18
M01011	12.2	1.080	128.4	228.9	164.4	1.57	2.79	2.01
M01012	77.3	1.014	25.6	69.0	34.5	1.98	5.33	2.67
Number of males	5	5	5	5	5	5	5	5
Mean	29.6	1.054	89.0	171.7	111.0	1.59	3.51	2.07
±S.D.	28.4	0.031	51.2	72.7	58.6	0.30	1.29	0.48

Turbidity, -: negative; +: slight

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA (100 mg/kg)

Male No.	Color	Turbidity	pH	Quality						Urinary sediments				
				Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03032	Light yellow	-	6.5	+	-	±	-	2+	±	+	-	-	±	±
M03033	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
M03034	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
M03035	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M03036	Light yellow	-	7.5	+	-	+	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M03032	19.2	1.046	69.7	181.2	89.4	1.34	3.48	1.72
M03033	23.4	1.041	67.0	155.9	70.9	1.57	3.65	1.66
M03034	18.8	1.048	75.4	166.9	101.3	1.42	3.14	1.90
M03035	22.5	1.044	83.4	165.0	91.1	1.88	3.71	2.05
M03036	18.2	1.059	96.8	165.7	119.3	1.76	3.02	2.17
Number of males	5	5	5	5	5	5	5	5
Mean	20.4	1.048	78.5	166.9	94.4	1.59	3.40	1.90
±S.D.	2.4	0.007	12.0	9.1	17.7	0.23	0.31	0.22

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

Turbidity, -: negative

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

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

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 23-2-3. Urinalysis in male rats of the recovery period

4-IBA (300/150 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04044	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M04045	Light yellow	-	7.0	+	-	-	-	-	±	-	-	-	±	-
M04046	Light yellow	-	7.5	±	-	-	-	-	±	-	-	-	±	-
M04047	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	-	-
M04048	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04044	19.1	1.045	85.6	192.4	108.0	1.63	3.67	2.06
M04045	28.5	1.038	74.2	137.4	88.0	2.11	3.92	2.51
M04046	63.4	1.015	30.8	78.6	38.6	1.95	4.98	2.45
M04047	25.0	1.039	57.7	151.9	78.5	1.44	3.80	1.96
M04048	30.2	1.033	63.3	138.8	73.2	1.91	4.19	2.21
Number of males	5	5	5	5	5	5	5	5
Mean	33.2	1.034	62.3	139.8	77.3	1.81	4.11	2.24
±S.D.	17.4	0.011	20.6	40.8	25.4	0.27	0.52	0.24

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

Turbidity, -: negative

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

Glucose, -: negative

Ketone, -: negative; ±: 5 ≤ and < 10 mg/dL; +: 10 ≤ and < 40 mg/dL; 2+: 40 ≤ and < 80 mg/dL

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	6.0	+	-	+	-	-	+	-	-	-	-	-
F05050	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	-	-
F05051	yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
F05052	Light yellow	-	6.5	±	-	±	-	-	±	-	-	-	±	-
F05053	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05049	6.2	1.070	135.1	215.8	130.8	0.84	1.34	0.81
F05050	10.4	1.047	68.2	143.0	96.1	0.71	1.49	1.00
F05051	5.1	1.086	144.4	227.3	200.5	0.74	1.16	1.02
F05052	18.3	1.036	66.5	136.9	81.6	1.22	2.51	1.49
F05053	11.8	1.062	105.9	211.8	142.7	1.25	2.50	1.68
Number of females	5	5	5	5	5	5	5	5
Mean	10.4	1.060	104.0	187.0	130.3	0.95	1.80	1.20
±S.D.	5.2	0.020	36.4	43.3	46.4	0.26	0.65	0.37

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 24-1-2. Urinalysis in female rats, satellite group

4-IBA (300/150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06060	Light yellow	-	6.5	-	-	±	-	-	±	-	-	-	-	-
F06061	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-
F06062	Light yellow	-	6.0	±	-	±	-	-	±	-	-	-	-	-
F06065	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
F06066	Light yellow	-	6.0	±	-	±	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06060	19.8	1.037	61.1	119.7	67.3	1.21	2.37	1.33
F06061	23.1	1.040	76.2	145.1	79.6	1.76	3.35	1.84
F06062	16.7	1.040	95.4	169.0	109.4	1.59	2.82	1.83
F06065	25.8	1.028	45.2	108.4	49.0	1.17	2.80	1.26
F06066	12.7	1.032	58.5	105.6	60.6	0.74	1.34	0.77
Number of females	5	5	5	5	5	5	5	5
Mean	19.6 *	1.035 *	67.3	129.6 *	73.2 *	1.29	2.54	1.41
±S.D.	5.2	0.005	19.2	27.0	23.1	0.40	0.75	0.45

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

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 24-2-1. Urinalysis in female rats of the recovery period

Control (vehicle: corn oil)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05054	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	-	-
F05055	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	-	-
F05056	Light yellow	-	8.0	±	-	-	-	-	±	-	-	-	±	-
F05057	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	±	-
F05058	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	9.0	1.079	146.0	231.0	183.9	1.31	2.08	1.66
F05055	16.1	1.041	79.1	144.5	86.7	1.27	2.33	1.40
F05056	13.0	1.028	51.3	82.2	27.4	0.67	1.07	0.36
F05057	17.9	1.041	93.8	149.2	90.8	1.68	2.67	1.63
F05058	8.8	1.079	174.4	220.2	211.3	1.53	1.94	1.86
Number of females	5	5	5	5	5	5	5	5
Mean	13.0	1.054	108.9	165.4	120.0	1.29	2.02	1.38
±S.D.	4.1	0.024	50.3	61.1	75.8	0.39	0.60	0.59

Turbidity, -: negative

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative

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

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA (300/150 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06065	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	-	-
F06066	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F06067	Light yellow	+	6.5	2+	-	-	-	2+	±	2+	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06065	35.5	1.029	62.6	128.5	74.2	2.22	4.56	2.63
F06066	10.9	1.043	83.9	140.5	66.2	0.91	1.53	0.72
F06067	24.1	1.035	76.1	145.4	86.1	1.83	3.50	2.08
Number of females	3	3	3	3	3	3	3	3
Mean	23.5	1.036	74.2	138.1	75.5	1.65	3.20	1.81
±S.D.	12.3	0.007	10.8	8.7	10.0	0.67	1.54	0.98

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

Turbidity, -: negative; +: slight

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

Glucose, -: negative

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

Bilirubin, -: negative

Occult blood, -: negative; ±: $0.03 \leq$ and < 0.06 mg/dL; +: $0.06 \leq$ and < 0.20 mg/dL; 2+: $0.20 \leq$ and < 1.00 mg/dLUrobilinogen, ±: normal; +: $2.0 \leq$ and < 4.0 mg/dL

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

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01001	774	13.7	39.2	50.6	17.7	34.9	89.9	16.1	22.7
M01002	823	15.0	42.5	51.6	18.2	35.3	103.3	15.0	25.1
M01003	806	14.6	42.0	52.1	18.1	34.8	98.2	18.2	25.1
M01004	869	15.9	44.5	51.2	18.3	35.7	112.8	18.4	29.4
M01005	769	14.0	40.1	52.1	18.2	34.9	117.0	13.7	21.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	808	14.6	41.7	51.5	18.1	35.1	104.2	16.3	24.8
S.D.	41	0.9	2.1	0.6	0.2	0.4	10.9	2.0	2.9

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	149.8	7.3	1.1	0.1	2.1	89.4	2.25
M01002	105.4	8.4	0.9	0.0	2.8	87.9	3.73
M01003	67.9	27.1	2.1	0.0	4.1	66.7	3.23
M01004	71.3	22.4	2.4	0.0	5.9	69.3	3.00
M01005	111.1	28.3	0.8	0.0	1.8	69.1	2.86
Number of males	5	5	5	5	5	5	5
Mean	101.1	18.7	1.5	0.0	3.3	76.5	3.01
S.D.	33.5	10.2	0.7	0.0	1.7	11.2	0.54

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 25-1-2. Hematological findings of male rats at the end of the dosing period

4-IBA (30 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M02013	847	14.9	42.7	50.4	17.6	34.9	90.5	15.1	23.9
M02014	878	15.3	44.0	50.1	17.4	34.8	93.3	19.4	25.8
M02015	789	14.4	42.0	53.2	18.3	34.3	99.3	15.5	24.7
M02016	816	14.7	43.3	53.1	18.0	33.9	103.0	19.2	26.7
M02017	888	15.8	46.3	52.1	17.8	34.1	107.8	17.9	25.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	844	15.0	43.7	51.8	17.8	34.4	98.8	17.4	25.4
S.D.	42	0.5	1.7	1.5	0.3	0.4	7.0	2.0	1.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M02013	108.9	15.6	1.2	0.1	3.2	79.9	2.88
M02014	104.9	15.7	1.3	0.0	3.1	79.9	3.80
M02015	63.6	16.0	1.6	0.0	3.8	78.6	2.31
M02016	83.2	23.1	1.3	0.0	4.2	71.4	3.96
M02017	91.1	23.5	1.2	0.1	3.0	72.2	2.50
Number of males	5	5	5	5	5	5	5
Mean	90.3	18.8	1.3	0.0	3.5	76.4	3.09
S.D.	18.2	4.1	0.2	0.1	0.5	4.2	0.75

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

4-IBA (100 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03025	798	14.8	42.5	53.3	18.5	34.8	95.8	13.8	22.8
M03026	828	14.4	41.6	50.2	17.4	34.6	101.2	15.9	25.4
M03027	811	14.6	43.6	53.8	18.0	33.5	94.4	16.7	23.0
M03028	778	14.4	41.3	53.1	18.5	34.9	112.0	16.5	24.1
M03029	825	14.3	40.9	49.6	17.3	35.0	106.2	13.6	20.6
Number of males	5	5	5	5	5	5	5	5	5
Mean	808	14.5	42.0	52.0	17.9	34.6	101.9	15.3	23.2
S.D.	21	0.2	1.1	1.9	0.6	0.6	7.3	1.5	1.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03025	103.2	19.0	0.4	0.1	3.9	76.6	2.65
M03026	104.0	23.2	1.1	0.0	3.5	72.2	2.37
M03027	59.7	18.9	1.5	0.0	4.7	74.9	3.49
M03028	59.8	20.0	1.2	0.0	2.7	76.1	2.70
M03029	113.8	29.8	1.0	0.0	3.6	65.6	4.45
Number of males	5	5	5	5	5	5	5
Mean	88.1	22.2	1.0	0.0	3.7	73.1	3.13
S.D.	26.2	4.6	0.4	0.0	0.7	4.5	0.85

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 25-1-4. Hematological findings of male rats at the end of the dosing period

4-IBA (300/150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04037	829	14.3	41.9	50.5	17.2	34.1	94.4	16.8	24.2
M04038	748	13.5	38.9	52.0	18.0	34.7	88.5	13.8	20.9
M04039	813	14.2	41.2	50.7	17.5	34.5	119.9	16.3	21.5
M04040	801	13.9	40.2	50.2	17.4	34.6	78.6	15.7	23.8
M04041	793	15.1	44.1	55.6	19.0	34.2	81.5	15.7	23.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	797	14.2	41.3	51.8	17.8	34.4	92.6	15.7	22.8
S.D.	30	0.6	1.9	2.2	0.7	0.3	16.5	1.1	1.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04037	84.9	11.9	0.5	0.0	3.3	84.3	3.32
M04038	85.8	14.8	0.7	0.0	2.9	81.6	3.61
M04039	94.0	12.2	1.3	0.0	2.9	83.6	2.63
M04040	54.1	20.2	0.9	0.0	3.9	75.0	3.06
M04041	84.2	9.6	1.4	0.0	5.5	83.5	3.62
Number of males	5	5	5	5	5	5	5
Mean	80.6	13.7	1.0	0.0	3.7	81.6	3.25
S.D.	15.3	4.1	0.4	0.0	1.1	3.8	0.42

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 25-2-1. Hematological findings of male rats at the end of the recovery period

Control (vehicle: corn oil)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M01008	830	14.8	42.4	51.1	17.8	34.9	109.7	17.3	28.1
M01009	952	16.0	44.2	46.4	16.8	36.2	118.2	25.1	32.4
M01010	881	15.9	44.6	50.6	18.0	35.7	125.4	21.7	28.0
M01011	807	14.5	41.4	51.3	18.0	35.0	117.9	16.9	30.2
M01012	812	15.4	43.2	53.2	19.0	35.6	119.3	17.2	30.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	856	15.3	43.2	50.5	17.9	35.5	118.1	19.6	29.8
S.D.	61	0.7	1.3	2.5	0.8	0.5	5.6	3.6	1.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	83.8	10.9	1.2	0.0	1.4	86.5	3.57
M01009	56.3	21.3	1.6	0.0	4.6	72.5	3.99
M01010	76.9	21.2	2.1	0.0	3.5	73.2	4.13
M01011	36.6	24.8	3.6	0.0	4.4	67.2	3.21
M01012	66.8	26.0	2.2	0.0	4.6	67.2	3.69
Number of males	5	5	5	5	5	5	5
Mean	64.1	20.8	2.1	0.0	3.7	73.3	3.72
S.D.	18.5	5.9	0.9	0.0	1.4	7.9	0.36

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA (100 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M03032	841	15.3	44.1	52.4	18.2	34.7	114.4	20.9	25.3
M03033	872	15.3	43.5	49.9	17.5	35.2	103.0	18.4	25.4
M03034	782	14.5	41.1	52.6	18.5	35.3	100.6	20.3	27.4
M03035	801	13.9	39.1	48.8	17.4	35.5	122.2	16.9	25.6
M03036	783	13.7	39.7	50.7	17.5	34.5	122.2	13.4	23.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	816	14.5	41.5	50.9	17.8	35.0	112.5	18.0	25.4 **
S.D.	39	0.8	2.2	1.6	0.5	0.4	10.3	3.0	1.5

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M03032	61.3	26.5	1.3	0.0	2.9	69.3	3.25
M03033	58.6	22.3	1.7	0.0	3.1	72.9	3.59
M03034	40.9	44.5	1.7	0.0	3.2	50.6	5.18
M03035	46.0	33.9	2.2	0.0	3.5	60.4	3.38
M03036	36.0	27.5	0.8	0.0	2.5	69.2	4.30
Number of males	5	5	5	5	5	5	5
Mean	48.6	30.9	1.5	0.0	3.0	64.5	3.94
S.D.	11.0	8.6	0.5	0.0	0.4	9.0	0.80

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 25-2-3. Hematological findings of male rats at the end of the recovery period

4-IBA (300/150 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
M04044	901	15.5	44.9	49.8	17.2	34.5	130.5	17.1	26.8
M04045	900	16.5	48.6	54.0	18.3	34.0	102.0	19.4	31.7
M04046	817	15.3	42.8	52.4	18.7	35.7	119.1	18.7	30.9
M04047	782	13.9	40.7	52.0	17.8	34.2	119.1	20.0	28.5
M04048	845	14.7	42.2	49.9	17.4	34.8	127.6	20.2	28.9
Number of males	5	5	5	5	5	5	5	5	5
Mean	849	15.2	43.8	51.6	17.9	34.6	119.7	19.1	29.4
S.D.	52	1.0	3.1	1.8	0.6	0.7	11.1	1.3	2.0

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
M04044	62.9	19.2	1.9	0.0	2.7	76.2	4.45
M04045	38.8	18.6	1.5	0.0	2.6	77.3	3.29
M04046	56.0	27.0	1.6	0.0	3.2	68.2	4.26
M04047	63.2	25.2	1.4	0.0	2.7	70.7	4.98
M04048	58.5	21.2	1.0	0.0	2.1	75.7	4.04
Number of males	5	5	5	5	5	5	5
Mean	55.9	22.2	1.5	0.0	2.7	73.6	4.20
S.D.	10.0	3.7	0.3	0.0	0.4	4.0	0.62

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F01003	687	12.9	40.3	58.7	18.8	32.0	142.3	12.5	19.9
F01007	697	13.4	40.3	57.8	19.2	33.3	113.8	13.1	21.7
F01009	742	13.7	40.3	54.3	18.5	34.0	128.7	12.9	22.4
F01011	653	12.8	37.5	57.4	19.6	34.1	115.9	12.3	19.5
F01012	628	12.1	36.6	58.3	19.3	33.1	96.8	12.8	19.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	681	13.0	39.0	57.3	19.1	33.3	119.5	12.7	20.7
S.D.	44	0.6	1.8	1.7	0.4	0.8	17.1	0.3	1.3

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F01003	124.6	21.8	0.4	0.0	5.1	72.7	15.58
F01007	114.3	34.7	0.5	0.0	1.5	63.3	5.98
F01009	92.6	14.9	0.8	0.0	3.6	80.7	4.30
F01011	99.3	24.4	0.6	0.0	2.9	72.1	7.91
F01012	78.4	21.5	0.5	0.0	4.7	73.3	8.48
Number of females	5	5	5	5	5	5	5
Mean	101.8	23.5	0.6	0.0	3.6	72.4	8.45
S.D.	18.1	7.2	0.2	0.0	1.4	6.2	4.31

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-1-2. Hematological findings of female rats at the end of the dosing period

4-IBA (30 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F02015	692	13.4	40.4	58.4	19.4	33.2	114.9	13.2	18.9
F02016	709	13.1	37.9	53.5	18.5	34.6	119.6	12.8	21.4
F02022	639	12.9	39.3	61.5	20.2	32.8	158.7	13.1	18.4
F02023	724	13.7	40.6	56.1	18.9	33.7	117.7	13.0	20.1
F02024	628	12.0	37.1	59.1	19.1	32.3	115.3	12.4	18.8
Number of females	5	5	5	5	5	5	5	5	5
Mean	678	13.0	39.1	57.7	19.2	33.3	125.2	12.9	19.5
S.D.	43	0.6	1.5	3.0	0.6	0.9	18.8	0.3	1.2

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F02015	117.2	40.2	0.3	0.0	3.9	55.6	5.24
F02016	110.8	36.0	0.3	0.0	4.4	59.3	2.83
F02022	116.6	35.1	0.2	0.0	3.2	61.5	9.03
F02023	107.6	29.7	1.0	0.0	3.1	66.2	5.42
F02024	117.2	41.1	0.3	0.0	3.4	55.2	9.45
Number of females	5	5	5	5	5	5	5
Mean	113.9	36.4 **	0.4	0.0	3.6	59.6 **	6.39
S.D.	4.4	4.6	0.3	0.0	0.5	4.5	2.80

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-1-3. Hematological findings of female rats at the end of the dosing period

4-IBA (100 mg/kg)

Female No.		RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
		($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F03025	#	773	14.2	42.1	54.5	18.4	33.7	86.3	11.6	17.9
F03027	#	765	14.2	40.7	53.2	18.6	34.9	94.5	12.5	21.9
F03030	#	736	14.3	41.1	55.8	19.4	34.8	92.8	12.1	21.9
F03032	#	765	14.2	40.9	53.5	18.6	34.7	89.2	13.3	18.8
F03034	#	723	13.5	38.5	53.3	18.7	35.1	94.6	12.2	22.8
Number of females		5	5	5	5	5	5	5	5	5
Mean		752	14.1	40.7	54.1	18.7	34.6	91.5	12.3	20.7
S.D.		22	0.3	1.3	1.1	0.4	0.5	3.6	0.6	2.2

Female No.		WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
		($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F03025	#	101.0	12.3	1.3	0.0	4.4	82.0	2.50
F03027	#	79.0	18.9	1.1	0.0	4.6	75.4	3.36
F03030	#	57.6	12.7	1.4	0.0	4.0	81.9	4.84
F03032	#	87.0	7.7	1.1	0.0	2.8	88.4	1.72
F03034	#	37.3	10.4	1.1	0.0	2.4	86.1	1.96
Number of females		5	5	5	5	5	5	5
Mean		72.4	12.4	1.2	0.0	3.6	82.8	2.88
S.D.		25.1	4.1	0.1	0.0	1.0	5.0	1.27

Non-pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

4-IBA (300/150 mg/kg)

Female No.		RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
		($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F04038	#	709	14.0	41.1	58.0	19.7	34.1	87.8	12.4	20.2
F04039	#	771	14.4	42.0	54.5	18.7	34.3	92.9	15.4	19.8
F04040	#	692	12.4	37.0	53.5	17.9	33.5	81.1	11.9	17.2
F04047	#	799	14.3	40.7	50.9	17.9	35.1	91.3	13.3	21.3
F04048	#	686	14.2	41.2	60.1	20.7	34.5	85.2	10.5	19.0
Number of females		5	5	5	5	5	5	5	5	5
Mean		731	13.9	40.4	55.4	19.0	34.3	87.7	12.7	19.5
S.D.		51	0.8	2.0	3.7	1.2	0.6	4.7	1.8	1.5

Female No.		WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
		($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F04038	#	70.9	16.4	0.4	0.1	2.0	81.1	4.04
F04039	#	98.0	5.7	0.2	0.0	4.0	90.1	1.91
F04040	#	90.6	11.5	1.0	0.0	2.3	85.2	4.29
F04047	#	62.2	11.0	1.0	0.0	5.0	83.0	2.05
F04048	#	56.6	14.6	1.1	0.2	3.9	80.2	2.65
Number of females		5	5	5	5	5	5	5
Mean		75.7	11.8	0.7	0.1	3.4	83.9	2.99
S.D.		18.0	4.1	0.4	0.1	1.3	4.0	1.11

Non-pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05049	752	14.5	41.1	54.7	19.3	35.3	96.7	12.8	20.3
F05050	744	14.3	40.1	53.9	19.2	35.7	113.3	11.7	20.7
F05051	806	15.0	41.6	51.6	18.6	36.1	123.0	12.5	19.6
F05052	683	13.5	38.3	56.1	19.8	35.2	119.6	12.0	19.8
F05053	828	13.8	38.8	46.9	16.7	35.6	116.8	12.6	19.7
Number of females	5	5	5	5	5	5	5	5	5
Mean	763	14.2	40.0	52.6	18.7	35.6	113.9	12.3	20.0
S.D.	57	0.6	1.4	3.6	1.2	0.4	10.2	0.5	0.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05049	49.2	8.2	1.6	0.0	2.0	88.2	3.46
F05050	85.4	8.1	1.1	0.0	2.7	88.1	2.63
F05051	124.9	8.9	0.7	0.0	2.3	88.1	2.87
F05052	68.4	5.7	1.2	0.0	2.9	90.2	2.78
F05053	72.5	12.4	1.5	0.0	3.3	82.8	5.09
Number of females	5	5	5	5	5	5	5
Mean	80.1	8.7	1.2	0.0	2.6	87.5	3.37
S.D.	28.2	2.4	0.4	0.0	0.5	2.8	1.01

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA (300/150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06060	754	14.2	40.8	54.1	18.8	34.8	99.0	14.6	21.5
F06061	731	13.8	39.7	54.3	18.9	34.8	95.4	12.7	17.9
F06062	766	14.4	42.6	55.6	18.8	33.8	64.2	12.8	17.7
Number of females	3	3	3	3	3	3	3	3	3
Mean	750	14.1	41.0	54.7	18.8	34.5 *	86.2 *	13.4	19.0
S.D.	18	0.3	1.5	0.8	0.1	0.6	19.1	1.1	2.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06060	70.3	7.6	0.9	0.1	2.1	89.3	1.93
F06061	172.7	15.2	0.8	0.0	2.0	82.0	4.21
F06062	81.8	14.5	0.9	0.0	2.1	82.5	2.97
Number of females	3	3	3	3	3	3	3
Mean	108.3	12.4	0.9	0.0	2.1	84.6	3.04
S.D.	56.1	4.2	0.1	0.1	0.1	4.1	1.14

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-3-1. Hematological findings of female rats at the end of the recovery period

Control (vehicle: corn oil)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F05054	768	14.5	40.6	52.9	18.9	35.7	103.2	12.2	21.9
F05055	765	14.3	41.7	54.5	18.7	34.3	112.1	11.6	20.8
F05056	787	14.8	42.5	54.0	18.8	34.8	108.0	11.8	22.7
F05057	792	15.4	43.0	54.3	19.4	35.8	99.3	11.8	24.5
F05058	852	15.6	44.0	51.6	18.3	35.5	107.6	12.4	22.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	793	14.9	42.4	53.5	18.8	35.2	106.0	12.0	22.6
S.D.	35	0.6	1.3	1.2	0.4	0.6	4.9	0.3	1.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	40.0	19.7	1.8	0.0	2.5	76.0	3.79
F05055	39.5	10.3	1.8	0.0	4.1	83.8	2.85
F05056	20.6	18.9	1.5	0.0	2.4	77.2	2.98
F05057	33.5	15.2	2.4	0.0	2.7	79.7	3.67
F05058	38.7	21.7	1.0	0.0	1.8	75.5	4.01
Number of females	5	5	5	5	5	5	5
Mean	34.5	17.2	1.7	0.0	2.7	78.4	3.46
S.D.	8.2	4.5	0.5	0.0	0.9	3.4	0.51

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 26-3-2. Hematological findings of female rats at the end of the recovery period

4-IBA (300/150 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu\text{L}$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu\text{L}$)	(sec)	(sec)
F06065	812	15.2	43.1	53.1	18.7	35.3	110.1	12.1	19.6
F06066	790	14.7	41.6	52.7	18.6	35.3	73.1	11.3	20.5
F06067	702	13.7	38.1	54.3	19.5	36.0	106.1	11.8	22.1
Number of females	3	3	3	3	3	3	3	3	3
Mean	768	14.5	40.9	53.4	18.9	35.5	96.4	11.7	20.7
S.D.	58	0.8	2.6	0.8	0.5	0.4	20.3	0.4	1.3

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu\text{L}$)	(%)	(%)	(%)	(%)	(%)	(%)
F06065	63.4	29.0	1.6	0.0	3.3	66.1	4.92
F06066	21.0	14.7	1.4	0.0	2.9	81.0	3.24
F06067	32.3	18.3	1.2	0.0	3.1	77.4	3.94
Number of females	3	3	3	3	3	3	3
Mean	38.9	20.7	1.4	0.0	3.1	74.8	4.03
S.D.	22.0	7.4	0.2	0.0	0.2	7.8	0.84

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

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	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.3	3.5	1.94	164	46	32	74	60	32	0	77	6.7	12	0.6	0.07	492
M01002	5.6	3.4	1.55	145	63	35	98	50	26	0	61	7.5	16	0.5	0.06	242
M01003	5.4	3.4	1.70	129	48	34	85	56	25	0	87	9.5	14	0.5	0.07	301
M01004	5.8	3.6	1.64	140	40	35	71	54	25	0	57	30.3	15	0.4	0.07	327
M01005	5.5	3.6	1.89	134	55	14	80	61	24	0	84	9.1	18	0.6	0.07	374
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.74	142	50	30	82	56	26	0	73	12.6	15	0.5	0.07	347
S.D.	0.2	0.1	0.17	14	9	9	11	4	3	0	14	10.0	2	0.1	0	94

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	6.3	9.2	138.9	4.28	101.4
M01002	6.6	9.6	139.2	4.16	101.7
M01003	5.4	9.5	138.9	4.15	102.9
M01004	6.4	9.9	138.8	4.03	103.0
M01005	5.3	9.4	138.5	3.59	103.2
Number of males	5	5	5	5	5
Mean	6.0	9.5	138.9	4.04	102.4
S.D.	0.6	0.3	0.3	0.27	0.8

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 27-1-2. Biochemical findings of male rats at the end of the dosing period

4-IBA 30 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M02013	5.3	3.4	1.79	147	48	39	84	53	27	1	53	10.1	12	0.4	0.07	469
M02014	4.9	3.2	1.88	150	40	19	70	56	25	0	55	10.3	13	0.4	0.06	390
M02015	5.3	3.3	1.65	157	45	16	75	48	22	0	65	18.0	14	0.5	0.08	245
M02016	5.1	3.2	1.68	152	40	24	76	51	23	0	69	15.6	14	0.4	0.06	257
M02017	6.3	3.7	1.42	162	48	34	83	58	27	0	97	8.8	15	0.5	0.09	537
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.4	1.68	154	44	26	78	53	25	0	68	12.6	14	0.4	0.07	380
S.D.	0.5	0.2	0.17	6	4	10	6	4	2	0	18	4.0	1	0.1	0.01	128
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	AN	AN	DU	AN	AN	DU	AN	AN	AN	KW	DU	AN	AN	AN

4-IBA 30 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	5.7	9.3	138.0	4.09	103.6
M02014	6.3	8.9	139.7	4.00	104.2
M02015	6.4	9.4	138.8	4.09	103.1
M02016	7.0	9.3	139.2	3.73	104.1
M02017	5.5	10.1	139.5	3.87	102.4
Number of males	5	5	5	5	5
Mean	6.2	9.4	139.0	3.96	103.5
S.D.	0.6	0.4	0.7	0.16	0.7
Significance	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 27-1-3. Biochemical findings of male rats at the end of the dosing period

4-IBA 100 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.7	3.5	1.59	158	47	14	85	77	41	0	87	91.7	14	0.6	0.10	514
M03026	5.4	3.5	1.84	153	29	24	60	50	30	0	88	20.9	18	0.5	0.07	353
M03027	5.2	3.4	1.89	165	34	27	72	73	33	0	74	10.0	19	0.6	0.07	514
M03028	5.6	3.3	1.43	140	36	22	61	59	26	0	103	7.6	18	0.5	0.06	370
M03029	5.6	3.6	1.80	151	50	16	80	69	25	0	89	8.4	18	0.5	0.07	399
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.71	153	39	21	72	66	31	0	88	27.7	17	0.5	0.07	430
S.D.	0.2	0.1	0.19	9	9	5	11	11	6	0	10	36.2	2	0.1	0.02	78
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	AN	AN	AN	DU	AN	AN	DU	AN	AN	AN	KW	DU	AN	AN	AN

4-IBA 100 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	6.4	9.7	137.7	4.13	101.0
M03026	6.0	9.4	139.6	4.24	102.1
M03027	5.9	9.4	139.1	4.07	104.6
M03028	5.5	9.5	139.9	3.89	104.0
M03029	6.1	9.4	139.3	3.64	104.6
Number of males	5	5	5	5	5
Mean	6.0	9.5	139.1	3.99	103.3
S.D.	0.3	0.1	0.8	0.24	1.6
Significance	NS	NS	NS	NS	NS
Statistical method	DU	DU	KW	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

4-IBA 300/150 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04037	5.2	3.2	1.60	142	39	25	70	80	37	0	153	9.6	18	0.6	0.07	353
M04038	5.1	3.3	1.83	155	41	22	74	67	32	0	78	31.2	17	0.5	0.07	284
M04039	5.2	3.4	1.89	159	38	14	69	69	26	0	67	43.7	20	0.5	0.09	450
M04040	5.3	3.6	2.12	147	33	25	67	69	19	0	98	49.8	20	0.5	0.06	500
M04041	4.9	3.2	1.88	171	29	11	53	70	35	0	115	16.1	20	0.6	0.07	372
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.1	3.3	1.86	155	36	19	67	71	30	0	102	30.1	19	0.5	0.07	392
S.D.	0.2	0.2	0.19	11	5	7	8	5	7	0	34	17.3	1	0.1	0.01	85
Significance	*	NS	NS	NS	*	NS	NS	**	NS	NS	NS	NS	**	NS	NS	NS
Statistical method	DT	AN	AN	AN	DU	AN	AN	DU	AN	AN	AN	KW	DU	AN	AN	AN

4-IBA 300/150 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	7.6	8.7	136.7	3.92	101.6
M04038	6.2	8.8	138.5	3.98	103.4
M04039	7.1	9.3	139.6	3.72	103.8
M04040	6.7	9.2	138.2	3.60	103.6
M04041	7.4	9.0	141.2	3.69	104.9
Number of males	5	5	5	5	5
Mean	7.0	9.0	138.8	3.78	103.5
S.D.	0.6	0.3	1.7	0.16	1.2
Significance	*	*	NS	NS	NS
Statistical method	DU	DU	KW	AN	AN

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

NS: Not significantly different from the control group.

DT: Analysis by Dunnett type mean rank test.

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 27-2-1. Biochemical findings of male rats at the end of the recovery period

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	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.3	3.4	1.79	145	56	14	81	47	21	0	113	6.5	16	0.5	0.05	271
M01009	6.1	3.7	1.54	133	60	21	89	70	23	0	377	8.3	20	0.7	0.06	218
M01010	6.1	3.7	1.54	143	55	26	91	58	24	0	67	16.1	17	0.5	0.05	273
M01011	5.6	3.5	1.67	122	47	24	72	72	24	0	170	7.0	16	0.5	0.04	353
M01012	5.2	3.3	1.74	105	55	10	79	65	29	0	72	11.6	15	0.5	0.06	253
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.5	1.66	130	55	19	82	62	24	0	160	9.9	17	0.5	0.05	274
S.D.	0.4	0.2	0.11	17	5	7	8	10	3	0	128	4.0	2	0.1	0.01	50

Control (vehicle: corn oil)					
Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	5.8	9.2	141.4	3.84	105.4
M01009	6.7	9.0	142.5	4.24	105.4
M01010	5.8	9.6	141.7	4.12	104.1
M01011	5.3	9.2	141.3	3.78	107.4
M01012	5.8	8.9	143.4	3.59	106.8
Number of males	5	5	5	5	5
Mean	5.9	9.2	142.1	3.91	105.8
S.D.	0.5	0.3	0.9	0.26	1.3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03032	4.8	3.3	2.20	115	60	17	82	56	23	0	100	7.7	21	0.5	0.04	243
M03033	5.5	3.4	1.62	151	46	21	78	69	32	0	69	8.2	16	0.6	0.06	337
M03034	5.4	3.4	1.70	126	42	11	66	76	39	0	59	7.6	16	0.5	0.04	263
M03035	5.2	3.3	1.74	112	53	10	74	76	27	0	226	9.4	20	0.6	0.04	249
M03036	5.8	3.6	1.64	135	78	16	111	65	26	0	124	10.7	19	0.6	0.06	283
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.4	1.78	128	56	15	82	68	29	0	116	8.7	18	0.6	0.05	275
S.D.	0.4	0.1	0.24	16	14	5	17	8	6	0	67	1.3	2	0.1	0.01	38
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

4-IBA 100 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03032	5.8	8.8	144.1	4.07	109.3
M03033	5.8	8.6	141.9	4.03	106.5
M03034	5.3	8.7	141.9	3.71	105.4
M03035	5.1	8.9	142.1	3.78	105.5
M03036	5.6	9.1	143.2	3.78	106.2
Number of males	5	5	5	5	5
Mean	5.5	8.8	142.6	3.87	106.6
S.D.	0.3	0.2	1.0	0.16	1.6
Significance	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 27-2-3. Biochemical findings of male rats at the end of the recovery period

4-IBA 300/150 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04044	5.5	3.5	1.75	118	56	14	82	51	19	0	194	7.4	19	0.5	0.05	221
M04045	5.9	3.7	1.68	161	44	13	72	57	28	0	88	10.9	23	0.6	0.05	279
M04046	5.5	3.4	1.62	140	53	18	81	60	30	0	56	36.4	14	0.5	0.06	249
M04047	5.3	3.5	1.94	127	49	18	76	62	22	0	194	7.5	21	0.6	0.05	201
M04048	5.7	3.5	1.59	115	54	15	79	58	24	0	83	8.9	20	0.5	0.05	280
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.5	1.72	132	51	16	78	58	25	0	123	14.2	19	0.5	0.05	246
S.D.	0.2	0.1	0.14	19	5	2	4	4	4	0	66	12.5	3	0.1	0.00	35
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

4-IBA 300/150 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04044	6.7	9.4	143.1	3.79	106.9
M04045	6.2	9.3	142.6	4.02	104.5
M04046	6.7	9.2	141.5	3.67	104.9
M04047	6.0	9.3	143.1	3.68	107.7
M04048	5.3	9.1	142.7	3.61	107.6
Number of males	5	5	5	5	5
Mean	6.2	9.3	142.6	3.75	106.3
S.D.	0.6	0.1	0.7	0.16	1.5
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

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	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01003	6.0	3.9	1.86	141	53	25	95	68	43	0	130	40.9	14	0.6	0.10	145
F01007	5.4	3.5	1.84	127	53	26	101	79	45	0	345	57.3	18	0.6	0.10	121
F01009	5.4	3.4	1.70	116	47	34	82	63	37	1	54	14.8	12	0.5	0.05	150
F01011	6.0	4.0	2.00	123	49	73	98	69	36	0	231	14.3	12	0.5	0.06	128
F01012	5.8	3.9	2.05	117	49	36	98	67	35	0	207	31.5	14	0.5	0.07	196
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.7	1.89	125	50	39	95	69	39	0	193	31.8	14	0.5	0.08	148
S.D.	0.3	0.3	0.14	10	3	20	7	6	4	0	110	18.2	2	0.1	0.02	29

Control (vehicle: corn oil)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01003	6.4	10.1	140.6	4.06	105.4
F01007	7.4	9.5	141.7	3.28	104
F01009	6.3	9.3	140.5	3.74	106.2
F01011	5.7	10.1	142	3.9	107.5
F01012	5.8	9.9	141.1	3.71	107.6
Number of females	5	5	5	5	5
Mean	6.3	9.8	141.2	3.74	106.1
S.D.	0.7	0.4	0.7	0.29	1.5

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-1-2. Biochemical findings of female rats at the end of the dosing period

4-IBA 30 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02015	5.5	3.5	1.75	146	62	19	121	76	30	0	229	15.7	13	0.5	0.06	187
F02016	5.1	3.1	1.55	131	39	14	76	79	34	0	61	9.4	9	0.5	0.07	231
F02022	5.0	3.2	1.78	133	42	16	92	82	28	1	285	31.8	14	0.5	0.08	160
F02023	5.5	3.8	2.24	140	48	16	107	63	35	0	59	14.2	10	0.5	0.09	155
F02024	5.7	3.7	1.85	150	53	54	112	69	44	1	277	10.7	7	0.5	0.07	145
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.5	1.83	140	49	24	102	74	34	0	182	16.4	11	0.5	0.07	176
S.D.	0.3	0.3	0.25	8	9	17	18	8	6	1	114	9.0	3	0.0	0.01	35
Significance	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	KW	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN

4-IBA 30 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02015	6.0	9.9	143.2	3.86	107.0
F02016	5.1	9.3	140.1	3.74	105.7
F02022	6.8	9.0	140.7	3.69	108.2
F02023	6.4	9.6	141.2	3.85	108.2
F02024	5.8	9.5	140.9	3.67	108.1
Number of females	5	5	5	5	5
Mean	6	9.5	141.2	3.76	107.4
S.D.	0.6	0.3	1.2	0.09	1.1
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

4-IBA 100 mg/kg

Female No.		Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03025	#	5.1	3.3	1.83	133	53	27	95	65	23	1	64	43.5	24	0.7	0.04	165
F03027	#	5.8	3.7	1.76	140	60	26	109	51	18	1	39	13.5	39	0.9	0.05	184
F03030	#	5.3	3.6	2.12	143	43	9	82	57	17	0	42	27.1	19	0.6	0.06	213
F03032	#	5.1	3.6	2.40	133	34	6	66	78	25	0	71	15.2	18	0.7	0.06	170
F03034	#	5.4	3.7	2.18	134	58	9	105	63	21	0	124	9.5	10	0.5	0.07	224
Number of females		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean		5.3	3.6	2.06	137	50	15	91	63	21	0	68	22	22	0.7	0.06	191
S.D.		0.3	0.2	0.26	5	11	10	18	10	3	1	34	14	11	0.1	0.01	26

4-IBA 100 mg/kg

Female No.		Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03025	#	5.5	9.1	142.9	3.13	105.7
F03027	#	6.9	9.4	141.6	3.59	105.2
F03030	#	5.0	8.9	142.3	3.20	109.2
F03032	#	5.6	8.7	140.7	3.23	104.6
F03034	#	3.9	8.8	143.6	3.46	111.2
Number of females		5	5	5	5	5
Mean		5.4	9.0	142.2	3.32	107.2
S.D.		1.1	0.3	1.1	0.19	2.9

Non-pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-1-4. Biochemical findings of female rats at the end of the dosing period

4-IBA 300/150 mg/kg

Female No.		Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F04038	#	5.6	3.5	1.67	151	71	11	122	66	31	0	33	15.7	12	0.6	0.06	226
F04039	#	5.1	3.4	2.00	122	65	18	105	70	19	1	103	9.4	11	0.6	0.06	165
F04040	#	5.4	3.5	1.84	139	66	26	116	76	32	1	186	9.9	14	0.7	0.05	196
F04047	#	5.5	3.6	1.89	119	48	14	88	68	26	1	125	13.2	15	0.5	0.05	268
F04048	#	5.8	3.8	1.90	148	63	52	113	50	19	2	140	9.5	14	0.6	0.05	221
Number of females		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean		5.5	3.6	1.86	136	63	24	109	66	25	1	117	12	13	0.6	0.05	215
S.D.		0.3	0.2	0.12	15	9	17	13	10	6	1	56	3	2	0.1	0.01	38

4-IBA 300/150 mg/kg

Female No.		Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04038	#	4.2	8.9	142.3	3.33	106.1
F04039	#	5.2	9.0	141.6	3.53	107.9
F04040	#	5.0	9.3	143.3	3.54	107.4
F04047	#	5.8	9.0	144.5	3.08	108.4
F04048	#	5.8	9.4	142.6	2.92	103.7
Number of females		5	5	5	5	5
Mean		5.2	9.1	142.9	3.28	106.7
S.D.		0.7	0.2	1.1	0.27	1.9

Non-pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

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	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	5.8	3.9	2.05	130	54	8	100	57	19	0	54	13.5	13	0.6	0.10	209
F05050	5.7	4.0	2.35	134	67	13	110	51	20	0	55	51.0	13	0.5	0.08	150
F05051	5.6	3.9	2.29	144	58	20	110	67	25	0	96	20.4	15	0.6	0.10	223
F05052	5.6	3.7	1.95	139	44	19	81	48	17	1	35	8.4	11	0.5	0.06	150
F05053	6.1	4.0	1.90	131	65	17	121	55	15	0	102	10.4	13	0.6	0.09	269
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.11	136	58	15	104	56	19	0	68	20.7	13	0.6	0.09	200
S.D.	0.2	0.1	0.2	6	9	5	15	7	4	0	29	17.5	1	0.1	0.02	51

Control (vehicle: corn oil)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.7	9.6	140.6	4.14	105.2
F05050	6.2	10.2	140.8	4.19	104.3
F05051	5.4	10	142.6	3.21	106.2
F05052	4.5	9.7	143.6	3.57	109.5
F05053	4.1	9.8	142.7	3.55	108.2
Number of females	5	5	5	5	5
Mean	5.2	9.9	142.1	3.73	106.7
S.D.	0.9	0.2	1.3	0.42	2.1

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06060	5.1	3.6	2.40	147	29	8	63	73	19	0	49	61.7	13	0.6	0.09	221
F06061	5.7	3.5	1.59	142	53	17	98	59	28	0	46	13.9	18	0.6	0.05	169
F06062	4.7	3.3	2.36	138	51	23	91	51	16	2	65	7.5	12	0.5	0.06	210
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	5.2	3.5	2.12	142	44	16	84	61	21	1	53	27.7	14	0.6	0.07	200
S.D.	0.5	0.2	0.46	5	13	8	19	11	6	1	10	29.6	3	0.1	0.02	27
Significance	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

4-IBA 300/150 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06060	6.3	9.1	138.5	3.97	104.2
F06061	6.9	9.5	140.3	3.96	102.5
F06062	5.6	8.8	141.6	3.42	108.3
Number of females	3	3	3	3	3
Mean	6.3	9.1	140.1	3.78	105
S.D.	0.7	0.4	1.6	0.31	3
Significance	NS	*	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

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	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	6.2	3.9	1.70	106	59	20	112	52	23	0	40	14.1	23	0.7	0.06	160
F05055	5.8	4.0	2.22	114	58	28	108	47	15	0	47	5.8	16	0.6	0.07	74
F05056	5.9	3.8	1.81	114	52	9	88	69	23	0	69	15.6	17	0.7	0.09	157
F05057	6.3	4.3	2.15	129	70	12	117	52	20	0	58	9.6	18	0.8	0.08	135
F05058	6	3.9	1.86	105	62	10	111	59	21	0	68	27.8	19	0.7	0.08	111
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.0	4.0	1.95	114	60	16	107	56	20	0	56	14.6	19	0.7	0.08	127
S.D.	0.2	0.2	0.23	10	7	8	11	9	3	0	13	8.3	3	0.1	0.01	36

Control (vehicle: corn oil)					
Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	4.1	9.0	141.6	3.59	107.8
F05055	3.6	9.2	142.7	3.39	108.8
F05056	3.7	8.9	142.9	3.46	110.0
F05057	5.1	9.5	140.6	4.02	106.4
F05058	3.0	8.8	142.6	3.23	108.8
Number of females	5	5	5	5	5
Mean	3.9	9.1	142.1	3.54	108.4
S.D.	0.8	0.3	1.0	0.3	1.3

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 28-3-2. Biochemical findings of female rats at the end of the recovery period

4-IBA 300/150 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ -GTP U/L	LDH U/L	Bile acid mg/dL	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06065	5.5	3.7	2.06	100	48	7	85	69	25	0	51	24.5	18	0.7	0.10	221
F06066	5.7	3.6	1.71	89	65	11	107	56	22	0	49	13.4	19	0.6	0.06	140
F06067	5.7	3.9	2.17	105	70	12	112	60	18	0	90	7.4	19	0.7	0.06	148
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	5.6	3.7	1.98	98	61	10	101	62	22	0	63	15.1	19	0.7	0.07	170
S.D.	0.1	0.2	0.24	8	12	3	14	7	4	0	23	8.7	1	0.1	0.02	45
Significance	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

4-IBA 300/150 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06065	5.2	9.1	140.8	3.51	104.0
F06066	5.3	9.0	141.4	4.22	107.3
F06067	4.7	9.3	141.9	3.35	108.4
Number of females	3	3	3	3	3
Mean	5.1	9.1	141.4	3.69	106.6
S.D.	0.3	0.2	0.6	0.46	2.3
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	423.1	2062.7	4.875	426.7	1.009	1185.2	2.801	12380.3	29.261	1419.5	3.355	1389.1	3.283	2808.6	6.638	635.9	1.503
M01002	496.9	1984.6	3.994	443.3	0.892	1429.3	2.876	13179.8	26.524	1610.7	3.241	1675.8	3.373	3286.5	6.614	694.5	1.398
M01003	462.9	1919.4	4.146	355.3	0.768	1432.2	3.094	12412.6	26.815	1664.8	3.596	1609.6	3.477	3274.4	7.074	740.4	1.599
M01004	505.8	2002.5	3.959	353.0	0.698	1663.8	3.289	13350.0	26.394	1554.3	3.073	1653.7	3.269	3208.0	6.342	785.8	1.554
M01005	482.2	2061.8	4.276	327.6	0.679	1489.7	3.089	12117.2	25.129	1430.3	2.966	1415.4	2.935	2845.7	5.901	1073.1	2.225
M01006	477.3	2076.9	4.351	300.9	0.630	1417.0	2.969	13680.8	28.663	1453.3	3.045	1437.3	3.011	2890.6	6.056	760.0	1.592
M01007	445.7	2035.0	4.566	358.6	0.805	1346.2	3.020	10495.1	23.547	1257.6	2.822	1268.6	2.846	2526.2	5.668	703.2	1.578
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	470.6	2020.4	4.310	366.5	0.783	1423.3	3.020	12516.5	26.619	1484.4	3.157	1492.8	3.171	2977.1	6.328	770.4	1.636
S.D.	29.0	55.8	0.326	51.2	0.132	144.4	0.160	1061.8	1.954	137.2	0.261	154.4	0.239	286.9	0.488	142.1	0.269

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)																		
Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M01001	551.6	1.304	674.6	1.594	1226.2	2.898	266.6	0.630	274.9	0.650	541.5	1.280	490.7	1.160	1710.2	4.042	16.8	0.040
M01002	1590.8	3.201	1498.2	3.015	3089.0	6.217	585.8	1.179	546.7	1.100	1132.5	2.279	794.4	1.599	1385.8	2.789	23.1	0.046
M01003	1619.7	3.499	1650.3	3.565	3270.0	7.064	587.5	1.269	574.9	1.242	1162.4	2.511	532.1	1.149	1755.7	3.793	22.2	0.048
M01004	1676.4	3.314	1606.7	3.177	3283.1	6.491	717.3	1.418	635.0	1.255	1352.3	2.674	606.1	1.198	1920.9	3.798	22.4	0.044
M01005	1701.0	3.528	1739.2	3.607	3440.2	7.134	624.6	1.295	603.3	1.251	1227.9	2.546	598.9	1.242	1461.6	3.031	18.1	0.038
M01006	1575.3	3.300	1557.6	3.263	3132.9	6.564	608.5	1.275	627.1	1.314	1235.6	2.589	616.2	1.291	1738.2	3.642	17.4	0.036
M01007	1738.1	3.900	1706.6	3.829	3444.7	7.729	560.8	1.258	567.0	1.272	1127.8	2.530	468.5	1.051	1067.0	2.394	21.0	0.047
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1493.3	3.149	1490.5	3.150	2983.7	6.300	564.4	1.189	547.0	1.155	1111.4	2.344	586.7	1.241	1577.1	3.356	20.1	0.043
S.D.	419.4	0.845	369.2	0.741	786.8	1.582	140.6	0.257	124.2	0.232	263.0	0.485	108.6	0.175	289.8	0.618	2.6	0.005

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	423.1	15.8	0.037	13.6	0.032	29.4	0.069
M01002	496.9	18.1	0.036	20.7	0.042	38.8	0.078
M01003	462.9	21.7	0.047	24.3	0.052	46.0	0.099
M01004	505.8	30.5	0.060	34.7	0.069	65.2	0.129
M01005	482.2	23.9	0.050	28.3	0.059	52.2	0.108
M01006	477.3	25.7	0.054	26.6	0.056	52.3	0.110
M01007	445.7	23.2	0.052	24.1	0.054	47.3	0.106
Number of males	7	7	7	7	7	7	7
Mean	470.6	22.7	0.048	24.6	0.052	47.3	0.100
S.D.	29.0	4.9	0.009	6.5	0.012	11.3	0.020

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-2. Organ weights of male rats at the end of the dosing period

4-IBA 30 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M02013	471.1	2099.2	4.456	275.3	0.584	1392.5	2.956	13154.7	27.923	1557.3	3.306	1552.6	3.296	3109.9	6.601	599.1	1.272
M02014	436.0	1855.9	4.257	169.5	0.389	1329.8	3.050	11993.0	27.507	1409.6	3.233	1423.0	3.264	2832.6	6.497	1057.0	2.424
M02015	442.1	2063.6	4.668	264.6	0.599	1303.7	2.949	12708.1	28.745	1479.0	3.345	1501.3	3.396	2980.3	6.741	581.8	1.316
M02016	464.3	2031.3	4.375	249.8	0.538	1390.9	2.996	13544.2	29.171	1514.4	3.262	1590.1	3.425	3104.5	6.686	665.9	1.434
M02017	512.0	2158.1	4.215	223.7	0.437	1476.1	2.883	15273.3	29.831	1471.7	2.874	1466.2	2.864	2937.9	5.738	701.2	1.370
M02018	513.3	1964.9	3.828	395.5	0.771	1360.6	2.651	14437.9	28.128	1462.0	2.848	1609.0	3.135	3071.0	5.983	988.0	1.925
M02019	467.0	2059.0	4.409	246.8	0.528	1510.7	3.235	14644.7	31.359	1774.1	3.799	1728.2	3.701	3502.3	7.500	957.7	2.051
M02020	406.8	2017.3	4.959	265.3	0.652	1380.6	3.394	10326.3	25.384	1503.5	3.696	1571.1	3.862	3074.6	7.558	817.7	2.010
M02021	449.1	2088.3	4.650	204.6	0.456	1478.5	3.292	12355.0	27.511	1597.4	3.557	1660.3	3.697	3257.7	7.254	710.0	1.581
M02022	479.7	2002.7	4.175	250.5	0.522	1382.7	2.882	12388.4	25.825	1570.5	3.274	1490.0	3.106	3060.5	6.380	710.9	1.482
M02023	480.4	1979.4	4.120	437.7	0.911	1280.1	2.665	12675.9	26.386	1394.6	2.903	1494.4	3.111	2889.0	6.014	812.0	1.690
M02024	510.4	1990.7	3.900	263.8	0.517	1524.9	2.988	15552.1	30.470	1695.2	3.321	1820.7	3.567	3515.9	6.889	803.3	1.574
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	469.4	2025.9	4.334	270.6	0.575	1400.9	2.995	13254.5	28.187	1535.8	3.285	1575.6	3.369	3111.4	6.653	783.7	1.677
S.D.	32.9	77.4	0.325	75.0	0.146	80.2	0.226	1511.8	1.832	111.9	0.305	115.6	0.296	217.0	0.585	152.3	0.354
Significance	NS	NS	NS	*	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

4-IBA 30 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M02013	1743.4	3.701	1630.8	3.462	3374.2	7.162	673.6	1.430	618.3	1.312	1291.9	2.742	344.1	0.730	1418.0	3.010	26.6	0.056
M02014	1290.5	2.960	1192.9	2.736	2483.4	5.696	615.4	1.411	537.9	1.234	1153.3	2.645	632.0	1.450	1762.3	4.042	21.4	0.049
M02015	1628.7	3.684	1718.9	3.888	3347.6	7.572	627.5	1.419	651.7	1.474	1279.2	2.893	439.7	0.995	1721.8	3.895	20.7	0.047
M02016	1872.9	4.034	1896.6	4.085	3769.5	8.119	592.3	1.276	595.9	1.283	1188.2	2.559	510.3	1.099	1451.3	3.126	28.4	0.061
M02017	1788.4	3.493	1763.7	3.445	3552.1	6.938	652.9	1.275	631.0	1.232	1283.9	2.508	607.2	1.186	1983.4	3.874	20.9	0.041
M02018	1431.4	2.789	1264.2	2.463	2695.6	5.252	495.9	0.966	465.5	0.907	961.4	1.873	618.3	1.205	1408.0	2.743	18.0	0.035
M02019	1566.5	3.354	1545.6	3.310	3112.1	6.664	589.9	1.263	649.9	1.392	1239.8	2.655	536.5	1.149	1436.5	3.076	19.2	0.041
M02020	1657.9	4.075	1576.6	3.876	3234.5	7.951	698.8	1.718	669.8	1.647	1368.6	3.364	585.0	1.438	1926.0	4.735	20.1	0.049
M02021	1516.7	3.377	1570.2	3.496	3086.9	6.874	613.7	1.367	627.8	1.398	1241.5	2.764	612.0	1.363	2228.5	4.962	16.0	0.036
M02022	1763.4	3.676	1764.8	3.679	3528.2	7.355	599.2	1.249	567.9	1.184	1167.1	2.433	665.5	1.387	2005.0	4.180	27.5	0.057
M02023	1764.7	3.673	1729.3	3.600	3494.0	7.273	659.2	1.372	672.6	1.400	1331.8	2.772	509.9	1.061	1466.7	3.053	19.7	0.041
M02024	1545.6	3.028	1643.9	3.221	3189.5	6.249	552.1	1.082	547.6	1.073	1099.7	2.155	646.3	1.266	1789.5	3.506	18.9	0.037
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1630.8	3.487	1608.1	3.438	3239.0	6.925	614.2	1.319	603.0	1.295	1217.2	2.614	558.9	1.194	1716.4	3.684	21.5	0.046
S.D.	168.5	0.405	204.0	0.468	365.1	0.858	55.2	0.188	62.5	0.192	111.9	0.371	95.0	0.209	280.2	0.716	3.9	0.009
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DU	DU	DU	DT	DU	DT	DU	DU	DU	DT	DU	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

4-IBA 30 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	471.1	20.7	0.044	22.7	0.048	43.4	0.092
M02014	436.0	23.5	0.054	22.2	0.051	45.7	0.105
M02015	442.1	26.3	0.059	25.8	0.058	52.1	0.118
M02016	464.3	22.2	0.048	20.7	0.045	42.9	0.092
M02017	512.0	26.0	0.051	25.8	0.050	51.8	0.101
M02018	513.3	16.8	0.033	26.3	0.051	43.1	0.084
M02019	467.0	23.6	0.051	24.6	0.053	48.2	0.103
M02020	406.8	25.9	0.064	26.5	0.065	52.4	0.129
M02021	449.1	23.1	0.051	24.2	0.054	47.3	0.105
M02022	479.7	21.4	0.045	19.4	0.040	40.8	0.085
M02023	480.4	25.1	0.052	24.9	0.052	50.0	0.104
M02024	510.4	26.4	0.052	26.3	0.052	52.7	0.103
Number of males	12	12	12	12	12	12	12
Mean	469.4	23.4	0.050	24.1	0.052	47.5	0.102
S.D.	32.9	2.9	0.008	2.4	0.006	4.3	0.013
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

4-IBA 100 mg/kg

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	455.2	1951.6	4.287	280.7	0.617	1188.3	2.611	16713.5	36.717	1472.8	3.236	1444.6	3.174	2917.4	6.409	843.0	1.852
M03026	411.5	1939.0	4.712	264.9	0.644	1306.1	3.174	14057.8	34.162	1478.7	3.593	1396.3	3.393	2875.0	6.987	720.3	1.750
M03027	456.7	1971.4	4.317	244.7	0.536	1368.7	2.997	15787.8	34.569	1275.1	2.792	1310.8	2.870	2585.9	5.662	683.8	1.497
M03028	486.2	2001.6	4.117	356.1	0.732	1497.2	3.079	15312.7	31.495	1590.8	3.272	1552.9	3.194	3143.7	6.466	821.1	1.689
M03029	500.5	1961.4	3.919	137.4	0.275	1610.6	3.218	16585.7	33.138	1696.5	3.390	1731.3	3.459	3427.8	6.849	1291.2	2.580
M03030	518.3	1890.5	3.648	299.3	0.577	1262.9	2.437	15421.8	29.755	1824.8	3.521	1778.7	3.432	3603.5	6.953	819.6	1.581
M03031	428.9	1996.9	4.656	285.5	0.666	1331.8	3.105	15010.3	34.997	1527.4	3.561	1544.7	3.602	3072.1	7.163	772.1	1.800
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	465.3	1958.9	4.237	266.9	0.578	1366.5	2.946	15555.7	33.548	1552.3	3.338	1537.0	3.303	3089.3	6.641	850.2	1.821
S.D.	38.5	37.8	0.381	66.8	0.148	143.8	0.301	919.5	2.321	175.9	0.278	171.3	0.243	344.3	0.512	202.9	0.356
Significance	NS	NS	NS	*	*	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

4-IBA 100 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M03025	1681.8	3.695	1647.3	3.619	3329.1	7.313	952.3	2.092	967.9	2.126	1920.2	4.218	461.2	1.013	1440.4	3.164	22.4	0.049
M03026	1542.0	3.747	1518.7	3.691	3060.7	7.438	638.3	1.551	731.8	1.778	1370.1	3.330	690.6	1.678	1587.3	3.857	20.8	0.051
M03027	1724.7	3.776	1652.6	3.619	3377.3	7.395	538.0	1.178	579.5	1.269	1117.5	2.447	338.5	0.741	1161.7	2.544	20.3	0.044
M03028	1796.3	3.695	1738.0	3.575	3534.3	7.269	687.2	1.413	681.2	1.401	1368.4	2.814	638.3	1.313	1638.1	3.369	23.4	0.048
M03029	1702.4	3.401	1680.9	3.358	3383.3	6.760	970.5	1.939	874.3	1.747	1844.8	3.686	498.5	0.996	1382.0	2.761	13.8	0.028
M03030	1760.4	3.396	1759.8	3.395	3520.2	6.792	715.0	1.380	841.1	1.623	1556.1	3.002	472.9	0.912	1507.2	2.908	23.0	0.044
M03031	1902.9	4.437	1939.3	4.522	3842.2	8.958	590.3	1.376	655.7	1.529	1246.0	2.905	553.6	1.291	1525.1	3.556	16.8	0.039
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1730.1	3.735	1705.2	3.683	3435.3	7.418	727.4	1.561	761.6	1.639	1489.0	3.200	521.9	1.135	1463.1	3.166	20.1	0.043
S.D.	110.8	0.347	129.3	0.390	238.1	0.734	170.3	0.332	137.4	0.281	300.8	0.596	117.8	0.314	158.0	0.463	3.6	0.008
Significance	NS	NS	NS	NS	NS	NS	NS	*	**	**	NS	**	NS	NS	NS	NS	NS	NS
Statistical method	DT	DU	DU	DU	DT	DU	DT	DU	DU	DU	DT	DU	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

4-IBA 100 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	455.2	22.7	0.050	26.4	0.058	49.1	0.108
M03026	411.5	22.5	0.055	22.3	0.054	44.8	0.109
M03027	456.7	19.7	0.043	19.3	0.042	39.0	0.085
M03028	486.2	25.8	0.053	26.0	0.053	51.8	0.107
M03029	500.5	24.6	0.049	26.7	0.053	51.3	0.102
M03030	518.3	25.1	0.048	25.4	0.049	50.5	0.097
M03031	428.9	21.3	0.050	24.3	0.057	45.6	0.106
Number of males	7	7	7	7	7	7	7
Mean	465.3	23.1	0.050	24.3	0.052	47.4	0.102
S.D.	38.5	2.2	0.004	2.7	0.005	4.6	0.009
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

4-IBA 300/150 mg/kg

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	413.8	1997.3	4.827	196.5	0.475	1164.5	2.814	17490.7	42.268	1421.9	3.436	1418.6	3.428	2840.5	6.864	698.3	1.688
M04038	483.7	1978.8	4.091	204.8	0.423	1466.2	3.031	17391.0	35.954	1638.0	3.386	1642.6	3.396	3280.6	6.782	1004.6	2.077
M04039	442.6	1984.6	4.484	226.6	0.512	1310.1	2.960	15559.4	35.155	1665.8	3.764	1685.8	3.809	3351.6	7.573	657.4	1.485
M04040	418.4	1971.8	4.713	172.5	0.412	1247.2	2.981	16094.5	38.467	1448.5	3.462	1447.8	3.460	2896.3	6.922	773.1	1.848
M04041	428.6	2003.3	4.674	324.1	0.756	1356.7	3.165	15212.6	35.494	1578.7	3.683	1491.2	3.479	3069.9	7.163	701.9	1.638
M04042	454.2	2050.8	4.515	329.1	0.725	1403.7	3.090	15803.1	34.793	1806.7	3.978	1700.0	3.743	3506.7	7.721	646.6	1.424
M04043	400.4	1895.7	4.735	157.0	0.392	1294.9	3.234	16062.5	40.116	1599.3	3.994	1553.5	3.880	3152.8	7.874	780.6	1.950
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	434.5	1983.2	4.577	230.1	0.528	1320.5	3.039	16230.5	37.464	1594.1	3.672	1562.8	3.599	3156.9	7.271	751.8	1.730
S.D.	28.2	46.5	0.246	69.6	0.151	99.9	0.140	880.4	2.879	131.3	0.254	115.1	0.203	241.9	0.446	122.8	0.240
Significance	NS	NS	NS	**	**	NS	NS	**	**	NS	**	NS	*	NS	**	NS	NS
Statistical method	AN	AN	AN	DU	DU	AN	AN	DU	DU	AN	DU	AN	DU	AN	DU	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

4-IBA 300/150 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M04037	652.9	1.578	691.9	1.672	1344.8	3.250	484.7	1.171	522.8	1.263	1007.5	2.435	457.0	1.104	1374.4	3.321	20.0	0.048
M04038	941.9	1.947	918.0	1.898	1859.9	3.845	397.5	0.822	408.5	0.845	806.0	1.666	599.7	1.240	1510.2	3.122	27.5	0.057
M04039	1044.0	2.359	1090.6	2.464	2134.6	4.823	472.6	1.068	376.7	0.851	849.3	1.919	563.2	1.272	1455.9	3.289	17.3	0.039
M04040	912.0	2.180	844.1	2.017	1756.1	4.197	382.2	0.913	414.8	0.991	797.0	1.905	460.9	1.102	1662.3	3.973	24.2	0.058
M04041	806.0	1.881	851.7	1.987	1657.7	3.868	532.2	1.242	504.6	1.177	1036.8	2.419	653.8	1.525	1410.1	3.290	22.7	0.053
M04042	1162.2	2.559	1221.3	2.689	2383.5	5.248	537.1	1.183	496.1	1.092	1033.2	2.275	458.2	1.009	1698.9	3.740	25.6	0.056
M04043	1063.0	2.655	1093.2	2.730	2156.2	5.385	453.4	1.132	402.3	1.005	855.7	2.137	422.2	1.054	1452.9	3.629	20.3	0.051
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	940.3	2.166	958.7	2.208	1899.0	4.374	465.7	1.076	446.5	1.032	912.2	2.108	516.4	1.187	1509.2	3.481	22.5	0.052
S.D.	171.5	0.389	183.4	0.416	352.1	0.798	60.1	0.154	59.1	0.157	108.7	0.290	88.4	0.177	124.8	0.305	3.6	0.007
Significance	NS	**	**	**	NS	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DT	DU	DU	DU	DT	DU	DT	DU	DU	DU	DT	DU	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

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

DU: Analysis by Dunnett's test.

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

4-IBA 300/150 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	413.8	21.6	0.052	25.4	0.061	47.0	0.114
M04038	483.7	18.0	0.037	20.5	0.042	38.5	0.080
M04039	442.6	22.1	0.050	21.2	0.048	43.3	0.098
M04040	418.4	23.6	0.056	26.7	0.064	50.3	0.120
M04041	428.6	19.9	0.046	20.3	0.047	40.2	0.094
M04042	454.2	30.3	0.067	30.8	0.068	61.1	0.135
M04043	400.4	20.3	0.051	19.3	0.048	39.6	0.099
Number of males	7	7	7	7	7	7	7
Mean	434.5	22.3	0.051	23.5	0.054	45.7	0.106
S.D.	28.2	4.0	0.009	4.3	0.010	8.0	0.018
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN	KW	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).

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-1. Organ weights of male rats at the end of the recovery period

Control (vehicle: corn oil)

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	483.5	2177.9	4.504	406.4	0.841	1455.5	3.010	11800.1	24.406	1632.5	3.376	1572.2	3.252	3204.7	6.628	890.1	1.841
M01009	518.8	2088.0	4.025	193.0	0.372	1474.8	2.843	12981.0	25.021	1563.2	3.013	1615.4	3.114	3178.6	6.127	782.1	1.508
M01010	579.4	2077.9	3.586	268.7	0.464	1512.0	2.610	16131.6	27.842	1597.6	2.757	1641.4	2.833	3239.0	5.590	894.7	1.544
M01011	521.1	2010.6	3.858	212.7	0.408	1444.3	2.772	13487.1	25.882	1582.3	3.036	1631.3	3.130	3213.6	6.167	946.0	1.815
M01012	502.4	1987.8	3.957	404.6	0.805	1403.2	2.793	13181.3	26.237	1605.5	3.196	1573.4	3.132	3178.9	6.327	882.9	1.757
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	521.0	2068.4	3.986	297.1	0.578	1458.0	2.806	13516.2	25.878	1596.2	3.076	1606.7	3.092	3203.0	6.168	879.2	1.693
S.D.	35.9	74.7	0.334	102.8	0.226	40.0	0.144	1595.7	1.312	25.9	0.230	32.3	0.155	25.4	0.378	59.7	0.156

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: corn oil)																		
Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M01008	1718.4	3.554	1700.2	3.516	3418.6	7.071	639.8	1.323	665.4	1.376	1305.2	2.699	289.2	0.598	1053.8	2.180	14.7	0.030
M01009	1409.7	2.717	1434.3	2.765	2844.0	5.482	524.7	1.011	542.3	1.045	1067.0	2.057	682.5	1.316	1704.2	3.285	20.2	0.039
M01010	1744.3	3.011	1770.3	3.055	3514.6	6.066	709.5	1.225	681.8	1.177	1391.3	2.401	557.6	0.962	1558.5	2.690	20.1	0.035
M01011	1808.4	3.470	1729.6	3.319	3538.0	6.789	714.2	1.371	677.9	1.301	1392.1	2.671	630.5	1.210	1847.8	3.546	21.4	0.041
M01012	1684.5	3.353	1701.0	3.386	3385.5	6.739	641.7	1.277	621.3	1.237	1263.0	2.514	756.5	1.506	1833.4	3.649	25.1	0.050
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1673.1	3.221	1667.1	3.208	3340.1	6.429	646.0	1.241	637.7	1.227	1283.7	2.468	583.3	1.118	1599.5	3.070	20.3	0.039
S.D.	154.1	0.349	133.2	0.299	284.6	0.645	76.6	0.140	58.5	0.126	133.4	0.260	179.7	0.351	326.6	0.621	3.7	0.007

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: corn oil)

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	483.5	23.4	0.048	27.3	0.056	50.7	0.105
M01009	518.8	26.6	0.051	28.1	0.054	54.7	0.105
M01010	579.4	27.8	0.048	27.4	0.047	55.2	0.095
M01011	521.1	22.2	0.043	23.8	0.046	46.0	0.088
M01012	502.4	27.3	0.054	26.3	0.052	53.6	0.107
Number of males	5	5	5	5	5	5	5
Mean	521.0	25.5	0.049	26.6	0.051	52.0	0.100
S.D.	35.9	2.5	0.004	1.7	0.004	3.8	0.008

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03032	433.2	1879.9	4.340	304.5	0.703	1323.7	3.056	10090.2	23.292	1448.1	3.343	1491.1	3.442	2939.2	6.785	652.6	1.506
M03033	451.5	1924.0	4.261	251.4	0.557	1364.4	3.022	12091.2	26.780	1457.7	3.229	1515.7	3.357	2973.4	6.586	793.3	1.757
M03034	428.2	2027.1	4.734	185.5	0.433	1454.4	3.397	11159.6	26.062	1436.4	3.355	1452.1	3.391	2888.5	6.746	670.9	1.567
M03035	514.8	2060.8	4.003	161.3	0.313	1357.0	2.636	11690.7	22.709	1543.3	2.998	1569.6	3.049	3112.9	6.047	776.3	1.508
M03036	483.8	1971.3	4.075	279.7	0.578	1272.8	2.631	13063.2	27.001	1585.5	3.277	1695.3	3.504	3280.8	6.781	843.9	1.744
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	462.3	1972.6	4.283	236.5	0.517	1354.5	2.948	11619.0	25.169	1494.2	3.240	1544.8	3.349	3039.0	6.589	747.4	1.616
S.D.	36.6	73.7	0.287	61.2	0.149	66.5	0.323	1102.5	2.020	66.2	0.145	94.3	0.176	158.8	0.314	82.3	0.125
Significance	*	NS	NS	NS	NS	*	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	AN	AN	AN	DU	AN	AN	AN	DU	AN	KW	AN	DT	AN	DU	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M03032	1620.4	3.741	1631.9	3.767	3252.3	7.508	617.1	1.425	951.3	2.196	1568.4	3.620	611.8	1.412	1839.6	4.247	15.1	0.035
M03033	1808.5	4.006	1775.9	3.933	3584.4	7.939	1063.2	2.355	676.7	1.499	1739.9	3.854	762.4	1.689	2521.8	5.585	11.6	0.026
M03034	1545.6	3.610	1576.2	3.681	3121.8	7.291	602.0	1.406	591.4	1.381	1193.4	2.787	706.7	1.650	1737.3	4.057	17.9	0.042
M03035	1735.2	3.371	1758.6	3.416	3493.8	6.787	598.9	1.163	596.1	1.158	1195.0	2.321	837.5	1.627	2050.9	3.984	20.0	0.039
M03036	1755.0	3.628	1666.6	3.445	3421.6	7.072	635.2	1.313	671.5	1.388	1306.7	2.701	561.8	1.161	1801.8	3.724	18.8	0.039
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1692.9	3.671	1681.8	3.648	3374.8	7.319	703.3	1.532	697.4	1.524	1400.7	3.057	696.0	1.508	1990.3	4.319	16.7	0.036
S.D.	107.2	0.231	84.6	0.219	186.6	0.437	201.7	0.471	147.5	0.395	243.6	0.651	111.4	0.222	319.5	0.732	3.4	0.006
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DT	DT	DU	DU	DU	DU	AN	AN	AN	DU	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).

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

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 100 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03032	433.2	23.7	0.055	23.6	0.054	47.3	0.109
M03033	451.5	21.0	0.047	22.1	0.049	43.1	0.095
M03034	428.2	19.0	0.044	22.5	0.053	41.5	0.097
M03035	514.8	26.1	0.051	28.5	0.055	54.6	0.106
M03036	483.8	27.1	0.056	31.0	0.064	58.1	0.120
Number of males	5	5	5	5	5	5	5
Mean	462.3	23.4	0.051	25.5	0.055	48.9	0.105
S.D.	36.6	3.4	0.005	4.0	0.006	7.2	0.010
Significance	*	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-3. Organ weights of male rats at the end of the recovery period

4-IBA 300/150 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	476.6	1904.3	3.996	340.2	0.714	1363.1	2.860	12328.1	25.867	1397.5	2.932	1449.8	3.042	2847.3	5.974	676.0	1.418
M04045	410.5	2035.2	4.958	256.4	0.625	1310.4	3.192	11026.4	26.861	1262.7	3.076	1219.3	2.970	2482.0	6.046	659.7	1.607
M04046	492.0	1866.9	3.795	403.9	0.821	1339.4	2.722	13221.7	26.873	1421.3	2.889	1489.2	3.027	2910.5	5.916	927.4	1.885
M04047	443.3	1911.9	4.313	344.4	0.777	1275.1	2.876	11421.7	25.765	1458.7	3.291	1689.8	3.812	3148.5	7.102	662.7	1.495
M04048	453.2	1891.5	4.174	212.6	0.469	1359.4	3.000	10699.6	23.609	1458.6	3.218	1455.0	3.211	2913.6	6.429	633.7	1.398
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	455.1	1922.0	4.247	311.5	0.681	1329.5	2.930	11739.5	25.795	1399.8	3.081	1460.6	3.212	2860.4	6.293	711.9	1.561
S.D.	31.4	65.6	0.442	76.3	0.140	36.9	0.177	1028.9	1.331	80.9	0.175	167.1	0.347	240.7	0.494	121.4	0.199
Significance	*	*	NS	NS	NS	**	NS	NS	NS	**	NS	NS	NS	*	NS	*	NS
Statistical method	DU	DU	AN	AN	AN	DU	AN	AN	AN	DU	AN	KW	AN	DT	AN	DU	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

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

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-3(continued). Organ weights of male rats at the end of the recovery period

4-IBA 300/150 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/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)
M04044	727.9	1.527	725.8	1.523	1453.7	3.050	388.3	0.815	383.7	0.805	772.0	1.620	542.9	1.139	1666.6	3.497	19.4	0.041
M04045	1029.4	2.508	1099.1	2.677	2128.5	5.185	446.4	1.087	469.9	1.145	916.3	2.232	609.5	1.485	1344.2	3.275	11.9	0.029
M04046	923.4	1.877	701.4	1.426	1624.8	3.302	440.1	0.895	369.1	0.750	809.2	1.645	821.8	1.670	1737.4	3.531	25.8	0.052
M04047	583.7	1.317	620.6	1.400	1204.3	2.717	481.4	1.086	544.6	1.229	1026.0	2.314	861.3	1.943	1802.1	4.065	29.1	0.066
M04048	793.3	1.750	840.8	1.855	1634.1	3.606	550.3	1.214	536.5	1.184	1086.8	2.398	925.8	2.043	1879.3	4.147	19.6	0.043
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	811.5	1.796	797.5	1.776	1609.1	3.572	461.3	1.019	460.8	1.023	922.1	2.042	752.3	1.656	1685.9	3.703	21.2	0.046
S.D.	172.6	0.452	186.1	0.535	338.6	0.959	59.8	0.161	82.4	0.227	135.3	0.378	166.6	0.364	206.6	0.382	6.6	0.014
Significance	**	**	**	**	**	**	*	NS	*	NS	*	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	DU	DU	DU	DU	DU	DT	DT	DU	DU	DU	DU	AN	AN	AN	DU	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).

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

DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 29-2-3(continued). Organ weights of male rats at the end of the recovery period

4-IBA 300/150 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04044	476.6	21.4	0.045	22.9	0.048	44.3	0.093
M04045	410.5	22.2	0.054	26.2	0.064	48.4	0.118
M04046	492.0	10.1	0.021	16.7	0.034	26.8	0.054
M04047	443.3	23.6	0.053	26.8	0.060	50.4	0.114
M04048	453.2	19.4	0.043	24.3	0.054	43.7	0.096
Number of males	5	5	5	5	5	5	5
Mean	455.1	19.3	0.043	23.4	0.052	42.7	0.095
S.D.	31.4	5.4	0.013	4.0	0.012	9.3	0.025
Significance	*	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	AN	AN

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

NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01002	280.5	1781.3	6.350	148.5	0.529	838.8	2.990	9821.6	35.015	927.3	3.306	895.3	3.192	1822.6	6.498	547.7	1.953
F01003	284.7	1860.1	6.534	117.7	0.413	947.2	3.327	9297.1	32.656	931.1	3.270	886.5	3.114	1817.6	6.384	627.9	2.205
F01004	369.4	1845.5	4.996	161.6	0.437	1066.3	2.887	11823.6	32.008	1123.4	3.041	1040.4	2.816	2163.8	5.858	870.4	2.356
F01005	271.6	1883.3	6.934	135.9	0.500	1022.6	3.765	9318.8	34.311	900.8	3.317	876.6	3.228	1777.4	6.544	674.1	2.482
F01006	328.8	1957.5	5.953	230.6	0.701	984.4	2.994	9173.0	27.898	872.5	2.654	817.0	2.485	1689.5	5.138	751.6	2.286
F01007	305.4	1927.0	6.310	152.4	0.499	1036.9	3.395	9915.8	32.468	869.0	2.845	914.2	2.993	1783.2	5.839	787.3	2.578
F01008	339.7	1930.8	5.684	175.1	0.515	1148.3	3.380	10209.6	30.055	1109.1	3.265	1066.9	3.141	2176.0	6.406	848.5	2.498
F01009	308.4	1949.0	6.320	190.9	0.619	961.8	3.119	9238.8	29.957	1053.2	3.415	1074.6	3.484	2127.8	6.899	595.9	1.932
F01010	280.1	1936.2	6.913	178.5	0.637	965.0	3.445	9509.6	33.951	882.0	3.149	845.8	3.020	1727.8	6.169	794.5	2.836
F01011	294.9	1825.7	6.191	218.2	0.740	942.4	3.196	9483.4	32.158	944.0	3.201	927.5	3.145	1871.5	6.346	648.7	2.200
F01012	310.5	1942.5	6.256	153.9	0.496	935.0	3.011	10298.6	33.168	938.2	3.022	925.9	2.982	1864.1	6.004	626.6	2.018
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	306.7	1894.4	6.222	169.4	0.553	986.2	3.228	9826.4	32.150	959.1	3.135	933.7	3.055	1892.8	6.190	706.7	2.304
S.D.	29.6	58.8	0.546	34.0	0.106	80.9	0.262	767.8	2.117	92.6	0.227	88.2	0.254	177.4	0.470	108.5	0.282

Control (vehicle: corn oil)

Control (Vehicle, cont'd)																		
Female No.		Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
			(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	#	276.3	1968.2	7.123	335.7	1.215	983.9	3.561	7876.8	28.508	962.5	3.484	915.1	3.312	1877.6	6.796	830.2	3.005
Number of females		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean		276.3	1968.2	7.123	335.7	1.215	983.9	3.561	7876.8	28.508	962.5	3.484	915.1	3.312	1877.6	6.796	830.2	3.005
S.D.																		

Non-pregnant

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-1(continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: corn oil)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01002	50.6	0.180	46.7	0.166	97.3	0.347	532.2	1.897	19.1	0.068	34.7	0.124	38.2	0.136	72.9	0.260
F01003	65.4	0.230	48.2	0.169	113.6	0.399	673.0	2.364	15.2	0.053	31.2	0.110	31.2	0.110	62.4	0.219
F01004	66.3	0.179	63.5	0.172	129.8	0.351	701.4	1.899	18.2	0.049	44.8	0.121	48.3	0.131	93.1	0.252
F01005	42.3	0.156	46.3	0.170	88.6	0.326	618.9	2.279	12.0	0.044	35.5	0.131	35.9	0.132	71.4	0.263
F01006	53.6	0.163	49.2	0.150	102.8	0.313	493.0	1.499	12.9	0.039	30.4	0.092	35.9	0.109	66.3	0.202
F01007	57.7	0.189	53.7	0.176	111.4	0.365	552.9	1.810	16.0	0.052	34.3	0.112	39.8	0.130	74.1	0.243
F01008	83.5	0.246	62.2	0.183	145.7	0.429	526.7	1.550	25.1	0.074	31.6	0.093	33.1	0.097	64.7	0.190
F01009	52.1	0.169	56.8	0.184	108.9	0.353	692.3	2.245	14.1	0.046	41.1	0.133	43.1	0.140	84.2	0.273
F01010	57.5	0.205	47.6	0.170	105.1	0.375	623.8	2.227	20.1	0.072	34.9	0.125	34.6	0.124	69.5	0.248
F01011	47.1	0.160	45.7	0.155	92.8	0.315	646.6	2.193	20.3	0.069	31.4	0.106	31.5	0.107	62.9	0.213
F01012	57.6	0.186	52.1	0.168	109.7	0.353	743.0	2.393	14.6	0.047	31.5	0.101	35.3	0.114	66.8	0.215
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	57.6	0.188	52.0	0.169	109.6	0.357	618.5	2.032	17.1	0.056	34.7	0.113	37.0	0.121	71.7	0.234
S.D.	11.2	0.029	6.4	0.010	16.3	0.035	82.2	0.318	3.9	0.013	4.5	0.014	5.1	0.014	9.4	0.028

Control (vehicle: corn oil)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	53.7	0.194	56.0	0.203	109.7	0.397	462.3	1.673	22.0	0.080	28.2	0.102	29.5	0.107	57.7	0.209
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean	53.7	0.194	56.0	0.203	109.7	0.397	462.3	1.673	22.0	0.080	28.2	0.102	29.5	0.107	57.7	0.209
S.D.																

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

4-IBA 30 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	315.1	1924.1	6.106	204.6	0.649	938.9	2.980	10728.3	34.047	1106.9	3.513	1075.3	3.413	2182.2	6.925	848.7	2.693
F02014	320.3	1872.2	5.845	158.1	0.494	1041.2	3.251	11870.5	37.061	1097.3	3.426	1070.7	3.343	2168.0	6.769	787.6	2.459
F02015	285.7	2034.7	7.122	115.8	0.405	949.9	3.325	11091.9	38.824	840.0	2.940	803.5	2.812	1643.5	5.753	567.4	1.986
F02016	246.2	1876.6	7.622	40.7	0.165	909.4	3.694	8809.2	35.781	750.6	3.049	736.8	2.993	1487.4	6.041	429.9	1.746
F02020	278.0	1925.1	6.925	144.5	0.520	915.3	3.292	14573.6	52.423	1206.4	4.340	1037.9	3.733	2244.3	8.073	685.3	2.465
F02021	301.3	1863.1	6.184	154.1	0.511	966.9	3.209	11290.3	37.472	903.9	3.000	822.5	2.730	1726.4	5.730	721.1	2.393
F02022	249.8	1789.7	7.165	56.9	0.228	872.5	3.493	10657.7	42.665	882.5	3.533	854.8	3.422	1737.3	6.955	621.6	2.488
F02023	308.6	1843.0	5.972	228.8	0.741	954.8	3.094	10772.1	34.906	911.0	2.952	932.2	3.021	1843.2	5.973	550.8	1.785
F02024	297.7	1871.2	6.286	122.3	0.411	909.8	3.056	12344.8	41.467	913.5	3.069	884.8	2.972	1798.3	6.041	527.8	1.773
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	289.2	1888.9	6.581	136.2	0.458	939.9	3.266	11348.7	39.405	956.9	3.314	913.2	3.160	1870.1	6.473	637.8	2.199
S.D.	26.9	68.2	0.634	61.4	0.183	47.8	0.223	1556.3	5.657	147.1	0.454	123.8	0.332	266.5	0.773	134.3	0.372
Significance	NS	NS	NS	NS	NS	NS	NS	*	**	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	AW	AW	TT	AW	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

4-IBA 30 mg/kg

Female No.		Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
			(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02018	#	289.1	1798.5	6.221	304.9	1.055	985.5	3.409	8954.8	30.975	932.0	3.224	927.7	3.209	1859.7	6.433	593.0	2.051
F02019	#	271.0	1909.4	7.046	225.4	0.832	802.1	2.960	8546.6	31.537	1048.4	3.869	999.5	3.688	2047.9	7.557	533.5	1.969
Number of females		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mean		280.1	1854.0	6.634	265.2	0.944	893.8	3.185	8750.7	31.256	990.2	3.547	963.6	3.449	1953.8	6.995	563.3	2.010
S.D.																		
# Non-pregnant																		

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-2(continued). Organ weights of female rats at the end of the dosing period

4-IBA 30 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	57.8	0.183	47.0	0.149	104.8	0.333	667.7	2.119	12.5	0.040	33.1	0.105	34.5	0.109	67.6	0.215
F02014	47.9	0.150	47.5	0.148	95.4	0.298	807.3	2.520	17.4	0.054	29.4	0.092	35.0	0.109	64.4	0.201
F02015	53.9	0.189	68.6	0.240	122.5	0.429	687.1	2.405	15.4	0.054	29.7	0.104	33.0	0.116	62.7	0.219
F02016	51.6	0.210	59.2	0.240	110.8	0.450	485.8	1.973	11.2	0.045	27.9	0.113	30.2	0.123	58.1	0.236
F02020	56.9	0.205	39.3	0.141	96.2	0.346	709.5	2.552	16.9	0.061	42.6	0.153	42.9	0.154	85.5	0.308
F02021	41.3	0.137	55.2	0.183	96.5	0.320	638.9	2.120	15.3	0.051	36.3	0.120	39.9	0.132	76.2	0.253
F02022	62.8	0.251	45.5	0.182	108.3	0.434	536.2	2.147	12.9	0.052	35.7	0.143	38.9	0.156	74.6	0.299
F02023	49.2	0.159	48.5	0.157	97.7	0.317	705.5	2.286	14.7	0.048	39.4	0.128	42.3	0.137	81.7	0.265
F02024	55.9	0.188	37.1	0.125	93.0	0.312	537.7	1.806	11.3	0.038	39.5	0.133	38.1	0.128	77.6	0.261
Number of females	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	53.0	0.186	49.8	0.174	102.8	0.360	641.7	2.214	14.2	0.049	34.8	0.121	37.2	0.129	72.0	0.251
S.D.	6.4	0.035	9.8	0.042	9.7	0.060	103.1	0.249	2.3	0.007	5.2	0.020	4.3	0.017	9.3	0.037
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

4-IBA 30 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02018	47.5	0.164	47.8	0.165	95.3	0.330	788.0	2.726	12.5	0.043	37.3	0.129	40.2	0.139	77.5	0.268
F02019	51.7	0.191	57.7	0.213	109.4	0.404	776.3	2.865	20.8	0.077	35.4	0.131	39.1	0.144	74.5	0.275
Number of females	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mean	49.6	0.178	52.8	0.189	102.4	0.367	782.2	2.796	16.7	0.060	36.4	0.130	39.7	0.142	76.0	0.272
S.D.																

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

4-IBA 100 mg/kg																		
Female No.		Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	#	285.8	1941.0	6.791	238.9	0.836	850.5	2.976	10427.5	36.485	1143.9	4.002	1025.9	3.590	2169.8	7.592	505.0	1.767
F03026	#	260.7	1804.2	6.921	292.0	1.120	824.1	3.161	9309.5	35.710	941.5	3.611	899.6	3.451	1841.1	7.062	642.1	2.463
F03027	#	259.3	1896.1	7.312	256.8	0.990	758.3	2.924	9525.9	36.737	946.4	3.650	926.9	3.575	1873.3	7.224	553.0	2.133
F03028	#	287.5	1804.3	6.276	205.8	0.716	967.3	3.365	11015.7	38.315	950.6	3.306	875.6	3.046	1826.2	6.352	647.0	2.250
F03029	#	261.7	1981.6	7.572	212.5	0.812	896.1	3.424	9200.8	35.158	891.3	3.406	874.2	3.340	1765.5	6.746	509.1	1.945
F03030	#	288.6	1872.8	6.489	346.8	1.202	998.1	3.458	10452.0	36.216	1026.3	3.556	1017.6	3.526	2043.9	7.082	604.6	2.095
F03031	#	261.8	1892.2	7.228	194.5	0.743	724.1	2.766	8668.1	33.110	813.0	3.105	837.9	3.201	1650.9	6.306	527.2	2.014
F03032	#	253.7	1903.4	7.503	270.7	1.067	779.0	3.071	9250.6	36.463	911.0	3.591	902.3	3.557	1813.3	7.147	487.6	1.922
F03033	#	272.2	1862.8	6.843	321.1	1.180	807.9	2.968	9328.4	34.270	1002.1	3.681	1015.6	3.731	2017.7	7.413	450.6	1.655
F03034	#	243.8	1814.7	7.443	219.6	0.901	799.9	3.281	9592.2	39.345	882.5	3.620	859.1	3.524	1741.6	7.144	541.5	2.221
F03035	#	300.8	1975.5	6.567	265.1	0.881	887.4	2.950	11531.3	38.335	1046.0	3.477	1006.7	3.347	2052.7	6.824	439.0	1.459
F03036	#	275.8	1784.2	6.469	216.6	0.785	855.6	3.102	10597.0	38.423	1235.6	4.480	1174.9	4.260	2410.5	8.740	511.8	1.856
Number of females		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean		271.0	1877.7	6.951	253.4	0.936	845.7	3.121	9908.3	36.547	982.5	3.624	951.4	3.512	1933.9	7.136	534.9	1.982
S.D.		17.0	67.0	0.450	48.0	0.171	81.6	0.220	869.3	1.845	117.8	0.347	98.1	0.301	213.2	0.634	67.4	0.277
# Non-pregnant																		

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-3(continued). Organ weights of female rats at the end of the dosing period

4-IBA 100 mg/kg																
Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	38.4	0.134	44.3	0.155	82.7	0.289	331.0	1.158	15.8	0.055	26.5	0.093	26.7	0.093	53.2	0.186
F03026	42.5	0.163	47.4	0.182	89.9	0.345	342.0	1.312	12.6	0.048	31.9	0.122	36.3	0.139	68.2	0.262
F03027	32.2	0.124	32.4	0.125	64.6	0.249	466.1	1.798	17.6	0.068	31.0	0.120	30.3	0.117	61.3	0.236
F03028	43.9	0.153	55.5	0.193	99.4	0.346	465.1	1.618	22.1	0.077	26.6	0.093	25.6	0.089	52.2	0.182
F03029	45.2	0.173	43.3	0.165	88.5	0.338	375.9	1.436	26.7	0.102	25.3	0.097	27.1	0.104	52.4	0.200
F03030	54.1	0.187	56.2	0.195	110.3	0.382	877.5	3.041	16.1	0.056	28.3	0.098	28.7	0.099	57.0	0.198
F03031	40.1	0.153	44.2	0.169	84.3	0.322	432.9	1.654	13.2	0.050	22.9	0.087	26.8	0.102	49.7	0.190
F03032	39.6	0.156	37.9	0.149	77.5	0.305	385.8	1.521	10.3	0.041	26.0	0.102	29.0	0.114	55.0	0.217
F03033	35.0	0.129	56.7	0.208	91.7	0.337	375.0	1.378	16.9	0.062	24.4	0.090	24.8	0.091	49.2	0.181
F03034	50.5	0.207	37.1	0.152	87.6	0.359	796.5	3.267	15.0	0.062	30.9	0.127	28.9	0.119	59.8	0.245
F03035	38.1	0.127	40.7	0.135	78.8	0.262	864.2	2.873	10.6	0.035	29.0	0.096	31.0	0.103	60.0	0.199
F03036	41.2	0.149	34.9	0.127	76.1	0.276	890.2	3.228	18.4	0.067	33.6	0.122	35.4	0.128	69.0	0.250
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	41.7	0.155	44.2	0.163	86.0	0.318	550.2	2.024	16.3	0.060	28.0	0.104	29.2	0.108	57.3	0.212
S.D.	6.1	0.025	8.4	0.027	11.8	0.041	231.5	0.819	4.7	0.018	3.3	0.015	3.6	0.015	6.6	0.029

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

4-IBA 300/150 mg/kg

Female No.		Body weight (g)	Brain (mg)	(mg/g)	Thymus (mg)	(mg/g)	Heart (mg)	(mg/g)	Liver (mg)	(mg/g)	Kidney (R) (mg)	(mg/g)	Kidney (L) (mg)	(mg/g)	Kidneys (mg)	(mg/g)	Spleen (mg)	(mg/g)
F04037	#	237.5	1723.6	7.257	275.7	1.161	701.8	2.955	9030.1	38.021	895.6	3.771	863.5	3.636	1759.1	7.407	445.0	1.874
F04038	#	246.1	1830.8	7.439	261.7	1.063	898.6	3.651	9633.4	39.144	805.1	3.271	792.4	3.220	1597.5	6.491	607.4	2.468
F04039	#	262.6	1829.1	6.965	301.1	1.147	876.2	3.337	10341.5	39.381	927.0	3.530	915.4	3.486	1842.4	7.016	616.9	2.349
F04040	#	270.6	1853.3	6.849	304.2	1.124	746.1	2.757	9635.3	35.607	784.1	2.898	784.3	2.898	1568.4	5.796	546.6	2.020
F04044	#	285.6	1933.5	6.770	213.5	0.748	1077.2	3.772	11708.6	40.996	1085.1	3.799	1108.8	3.882	2193.9	7.682	647.4	2.267
F04045	#	300.2	1993.1	6.639	222.8	0.742	990.7	3.300	12385.7	41.258	1290.4	4.298	1205.6	4.016	2496.0	8.314	809.7	2.697
F04047	#	214.2	1801.9	8.412	215.4	1.006	751.3	3.507	8830.9	41.227	894.1	4.174	835.6	3.901	1729.7	8.075	405.1	1.891
F04048	#	275.2	1864.5	6.775	318.5	1.157	942.6	3.425	11726.7	42.612	1045.0	3.797	973.7	3.538	2018.7	7.335	539.0	1.959
Number of females		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean		261.5	1853.7	7.138	264.1	1.019	873.1	3.338	10411.5	39.781	965.8	3.692	934.9	3.572	1900.7	7.265	577.1	2.191
S.D.		27.8	81.6	0.580	42.6	0.177	131.6	0.340	1359.0	2.231	167.5	0.457	152.8	0.377	318.3	0.826	125.9	0.302
# Non-pregnant																		

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-1-4(continued). Organ weights of female rats at the end of the dosing period

4-IBA 300/150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	30.3	0.128	32.7	0.138	63.0	0.265	369.1	1.554	13.6	0.057	21.0	0.088	20.7	0.087	41.7	0.176
F04038	38.0	0.154	27.4	0.111	65.4	0.266	952.3	3.870	19.3	0.078	29.0	0.118	28.1	0.114	57.1	0.232
F04039	41.7	0.159	36.3	0.138	78.0	0.297	348.9	1.329	18.7	0.071	31.1	0.118	30.8	0.117	61.9	0.236
F04040	34.9	0.129	37.2	0.137	72.1	0.266	457.4	1.690	10.7	0.040	23.4	0.086	25.8	0.095	49.2	0.182
F04044	53.6	0.188	45.1	0.158	98.7	0.346	525.3	1.839	15.6	0.055	31.3	0.110	35.4	0.124	66.7	0.234
F04045	47.6	0.159	44.0	0.147	91.6	0.305	637.6	2.124	15.5	0.052	28.4	0.095	30.0	0.100	58.4	0.195
F04047	31.1	0.145	32.8	0.153	63.9	0.298	287.7	1.343	5.1	0.024	24.0	0.112	28.5	0.133	52.5	0.245
F04048	47.4	0.172	49.9	0.181	97.3	0.354	563.7	2.048	15.8	0.057	27.1	0.098	33.8	0.123	60.9	0.221
Number of females	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	40.6	0.154	38.2	0.145	78.8	0.300	517.8	1.975	14.3	0.054	26.9	0.103	29.1	0.112	56.1	0.215
S.D.	8.5	0.020	7.5	0.020	15.1	0.035	211.3	0.820	4.6	0.017	3.8	0.013	4.6	0.016	8.0	0.027

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	254.5	1900.8	7.469	263.6	1.036	911.4	3.581	6682.9	26.259	747.2	2.936	702.3	2.760	1449.5	5.695	501.7	1.971
F05050	319.4	1972.1	6.174	338.5	1.060	919.3	2.878	7735.5	24.219	989.3	3.097	977.2	3.059	1966.5	6.157	686.5	2.149
F05051	287.2	1978.1	6.888	254.7	0.887	916.6	3.192	7169.9	24.965	857.4	2.985	836.5	2.913	1693.9	5.898	612.6	2.133
F05052	318.8	1963.0	6.157	396.5	1.244	918.0	2.880	7960.8	24.971	949.4	2.978	942.4	2.956	1891.8	5.934	570.0	1.788
F05053	279.7	1940.2	6.937	331.7	1.186	1063.0	3.801	7003.7	25.040	881.7	3.152	829.6	2.966	1711.3	6.118	601.7	2.151
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	291.9	1950.8	6.725	317.0	1.083	945.7	3.266	7310.6	25.091	885.0	3.030	857.6	2.931	1742.6	5.960	594.5	2.038
S.D.	27.6	31.5	0.559	58.6	0.139	65.7	0.415	527.1	0.734	93.3	0.091	108.2	0.109	201.0	0.186	67.2	0.159

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-2-1(continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: corn oil)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	52.4	0.206	45.6	0.179	98.0	0.385	457.2	1.796	17.9	0.070	31.6	0.124	33.3	0.131	64.9	0.255
F05050	50.8	0.159	62.1	0.194	112.9	0.353	355.3	1.112	10.3	0.032	29.3	0.092	30.7	0.096	60.0	0.188
F05051	40.3	0.140	50.4	0.175	90.7	0.316	507.6	1.767	16.4	0.057	26.1	0.091	27.1	0.094	53.2	0.185
F05052	64.8	0.203	93.2	0.292	158.0	0.496	434.1	1.362	13.4	0.042	28.8	0.090	29.4	0.092	58.2	0.183
F05053	47.1	0.168	39.2	0.140	86.3	0.309	1019.5	3.645	17.4	0.062	30.7	0.110	33.6	0.120	64.3	0.230
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	51.1	0.175	58.1	0.196	109.2	0.372	554.7	1.936	15.1	0.053	29.3	0.101	30.8	0.107	60.1	0.208
S.D.	9.0	0.029	21.3	0.057	29.1	0.076	265.6	0.997	3.2	0.015	2.1	0.015	2.7	0.018	4.8	0.033

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

4-IBA 300/150 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06060	250.7	1791.7	7.147	211.1	0.842	872.1	3.479	10700.6	42.683	913.6	3.644	859.3	3.428	1772.9	7.072	424.9	1.695
F06061	297.8	1895.0	6.363	353.1	1.186	842.2	2.828	11029.8	37.038	1014.9	3.408	1015.8	3.411	2030.7	6.819	649.9	2.182
F06062	274.3	1777.4	6.480	261.8	0.954	915.1	3.336	10793.9	39.351	931.0	3.394	967.0	3.525	1898.0	6.919	626.5	2.284
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	274.3	1821.4	6.663	275.3	0.994	876.5	3.214	10841.4	39.691	953.2	3.482	947.4	3.455	1900.5	6.937	567.1	2.054
S.D.	23.6	64.2	0.423	72.0	0.175	36.6	0.342	169.7	2.838	54.2	0.140	80.1	0.062	128.9	0.127	123.7	0.315
Significance	NS	**	NS	NS	NS	NS	NS	**	**	NS	**	NS	**	NS	**	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-2-2(continued). Organ weights of female rats at the end of the dosing period, satellite group

4-IBA 300/150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06060	41.0	0.164	29.4	0.117	70.4	0.281	377.3	1.505	14.9	0.059	34.6	0.138	39.3	0.157	73.9	0.295
F06061	59.2	0.199	48.6	0.163	107.8	0.362	559.2	1.878	19.5	0.065	28.7	0.096	33.8	0.113	62.5	0.210
F06062	30.7	0.112	45.6	0.166	76.3	0.278	619.0	2.257	15.0	0.055	37.3	0.136	35.9	0.131	73.2	0.267
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	43.6	0.158	41.2	0.149	84.8	0.307	518.5	1.880	16.5	0.060	33.5	0.123	36.3	0.134	69.9	0.257
S.D.	14.4	0.044	10.3	0.027	20.1	0.048	125.9	0.376	2.6	0.005	4.4	0.024	2.8	0.022	6.4	0.043
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	*	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: corn oil)

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	353.2	1897.6	5.373	308.4	0.873	1043.6	2.955	7993.4	22.631	962.1	2.724	965.0	2.732	1927.1	5.456	496.8	1.407
F05055	292.2	1823.6	6.241	262.2	0.897	909.6	3.113	7190.7	24.609	838.9	2.871	813.2	2.783	1652.1	5.654	548.7	1.878
F05056	282.9	1939.2	6.855	287.2	1.015	821.6	2.904	6584.9	23.276	825.4	2.918	772.7	2.731	1598.1	5.649	552.4	1.953
F05057	308.3	1994.9	6.471	232.5	0.754	1145.7	3.716	7646.5	24.802	943.0	3.059	925.4	3.002	1868.4	6.060	573.0	1.859
F05058	294.8	1940.0	6.581	226.4	0.768	922.0	3.128	8022.1	27.212	976.0	3.311	983.5	3.336	1959.5	6.647	508.2	1.724
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	306.3	1919.1	6.304	263.3	0.861	968.5	3.163	7487.5	24.506	909.1	2.977	892.0	2.917	1801.0	5.893	535.8	1.764
S.D.	27.8	63.6	0.565	35.1	0.106	126.7	0.324	606.2	1.764	71.4	0.222	93.9	0.260	165.0	0.475	32.0	0.216

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-3-1(continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: corn oil)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	47.8	0.135	46.3	0.131	94.1	0.266	401.0	1.135	21.3	0.060	30.2	0.086	34.0	0.096	64.2	0.182
F05055	47.8	0.164	50.4	0.172	98.2	0.336	621.3	2.126	19.4	0.066	31.8	0.109	31.3	0.107	63.1	0.216
F05056	57.7	0.204	58.6	0.207	116.3	0.411	853.6	3.017	17.7	0.063	31.3	0.111	36.9	0.130	68.2	0.241
F05057	45.5	0.148	49.8	0.162	95.3	0.309	504.6	1.637	22.3	0.072	12.0	0.039	4.6	0.015	16.6	0.054
F05058	47.3	0.160	48.7	0.165	96.0	0.326	1338.0	4.539	21.6	0.073	35.9	0.122	37.7	0.128	73.6	0.250
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	49.2	0.162	50.8	0.167	100.0	0.330	743.7	2.491	20.5	0.067	28.2	0.093	28.9	0.095	57.1	0.189
S.D.	4.8	0.026	4.7	0.027	9.2	0.053	372.4	1.339	1.9	0.006	9.3	0.033	13.8	0.047	23.0	0.080

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

4-IBA 300/150 mg/kg

Female No.	Body weight (g)	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06065	276.8	1858.4	6.714	353.3	1.276	771.7	2.788	7018.5	25.356	849.2	3.068	816.4	2.949	1665.6	6.017	542.7	1.961
F06066	230.6	1826.8	7.922	380.1	1.648	809.0	3.508	6207.2	26.918	823.2	3.570	755.8	3.278	1579.0	6.847	449.4	1.949
F06067	272.3	1875.2	6.887	326.1	1.198	867.7	3.187	8001.2	29.384	945.5	3.472	1156.8	4.248	2102.3	7.721	527.1	1.936
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	259.9	1853.5	7.174	353.2	1.374	816.1	3.161	7075.6	27.219	872.6	3.370	909.7	3.492	1782.3	6.862	506.4	1.949
S.D.	25.5	24.6	0.653	27.0	0.240	48.4	0.361	898.4	2.031	64.4	0.266	216.2	0.675	280.5	0.852	50.0	0.013
Significance	NS	NS	NS	**	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 30-3-2(continued). Organ weights of female rats at the end of the recovery period

4-IBA 300/150 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06065	35.5	0.128	26.5	0.096	62.0	0.224	357.0	1.290	12.4	0.045	29.5	0.107	33.9	0.122	63.4	0.229
F06066	47.6	0.206	53.8	0.233	101.4	0.440	416.8	1.807	15.1	0.065	28.0	0.121	26.6	0.115	54.6	0.237
F06067	38.0	0.140	50.7	0.186	88.7	0.326	470.7	1.729	13.6	0.050	26.8	0.098	50.7	0.186	77.5	0.285
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	40.4	0.158	43.7	0.172	84.0	0.330	414.8	1.609	13.7	0.053	28.1	0.109	37.1	0.141	65.2	0.250
S.D.	6.4	0.042	14.9	0.070	20.1	0.108	56.9	0.279	1.4	0.010	1.4	0.012	12.4	0.039	11.6	0.030
Significance	NS	NS	NS	NS	NS	NS	NS	NS	**	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	AW	TT	TT	TT	TT	TT

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

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

Findings	Group	4-IBA							4-IBA								4-IBA							4-IBA													
	Dose(mg/kg)	0							30								100							300/150													
	Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043			
Thyroid gland																																					
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-			
Liver																																					
Discoloration, pale colored		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	P	-			
Enlargement		-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	-	-	P	P	-	P	P	P	P			
Kidney																																					
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-			
Spleen																																					
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	P	-	-	-	-	-	-			
Adrenal gland																																					
Small, bilateral		P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Testis																																					
Edematous, bilateral		P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	P			
Enlargement, bilateral		-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-			
Small, bilateral		P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	P	P	P	P	P			
Epididymis																																					
Enlargement		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	P	-	-			
Nodule, whitish, caudal, bilateral/unilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	P	-	-	P	-	-	-	-	-	-			
Small, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-	-	-	-	P			
Notes) -: No abnormal changes P: Non-graded change																																					

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA					4-IBA				
	Dose(mg/kg)	0					100					300/150				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M03 032	M03 033	M03 034	M03 035	M03 036	M04 044	M04 045	M04 046	M04 047	M04 048
Testis																
Edematous, bilateral		-	-	-	-	-	-	-	-	-	-	-	P	-	P	P
Small, bilateral		-	-	-	-	-	-	-	-	-	-	P	P	P	P	P
Epididymis																
Edematous, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Nodule, whitish, caudal, bilateral/unilateral		-	-	-	-	-	P	P	-	-	-	-	-	-	-	-
Small, bilateral		-	-	-	-	-	-	-	-	-	-	P	-	P	P	P

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 32-1. Macroscopic findings of female rats at the end of the dosing period

[illegible]

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

Fate: blank, Subjected to autopsy on day 5 of lactation; D, died; NP, not pregnant; TL, total litter loss

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group Dose(mg/kg)	Animal No.	4-IBA 0					4-IBA 300/150							
			F050	F050	F050	F050	F050	F060	F060	F060	F060	F060	F060	F060	F060
			49	50	51	52	53	59	60	61	62	63	64	65	68
			Fate					D				S			
Pituitary gland															
Discoloration, dark colored			-	-	-	-	-	-	-	-	-	-	-	-	P
Thyroid gland															
Discoloration, dark colored			-	-	-	-	-	-	-	-	-	-	-	-	P
Thymus															
Small			-	-	-	-	-	P	-	-	-	P	P	-	-
Lung															
Dark reddish area			-	-	-	-	-	P	-	-	-	-	-	-	P
Liver															
Discoloration, pale colored			-	-	-	-	-	P	P	-	-	-	P	-	-
Enlargement			-	-	-	-	-	P	P	P	P	P	P	P	P
Stomach															
Dark colored spot/area, mucosa, glandular stomach			-	-	-	-	-	-	P	-	-	-	-	-	-
Edematous, mucosa, forestomach			-	-	-	-	-	-	-	-	P	-	-	-	-
Small intestine															
Retention, watery content			-	-	-	-	-	P	-	-	-	-	-	-	-
Retention, with black content			-	-	-	-	-	-	-	-	-	-	P	-	P
Kidney															
Enlargement			-	-	-	-	-	-	-	-	-	P	-	-	-
Dark colored area, bilateral			-	-	-	-	-	-	-	-	-	-	-	-	P
Rough surface, bilateral			-	-	-	-	-	-	-	-	-	-	P	-	-
Spleen															
Discoloration, pale colored			-	-	-	-	-	P	-	-	-	-	P	-	-
Small			-	-	-	-	-	P	-	-	-	P	P	P	P
Adrenal gland															
Enlargement, bilateral			-	-	-	-	-	-	-	-	-	P	P	-	-
Hair															
Soiled fur, perinasal/ perineal area/region			-	-	-	-	-	P	-	-	-	-	P	-	-

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

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA		
	Dose(mg/kg)	0					300/150		
	Animal No.	F050	F050	F050	F050	F050	F060	F060	F060
		54	55	56	57	58	65	66	67
	Fate								
Adrenal gland									
Small, bilateral		-	-	-	P	-	-	-	-

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

Fate: blank, Subjected to autopsy on schedule

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-1. Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg) Animal No.	4-IBA 0					4-IBA 30					4-IBA 100					4-IBA 300/150							
		M01 001	M01 002	M01 003	M01 004	M01 005	M02 013	M02 014	M02 015	M02 016	M02 017	M03 025	M03 026	M03 027	M03 028	M03 029	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043	
Brain		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Spinal cord		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Pituitary gland							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Remnant, Rathke's pouch	P	-	-	-	-	-											-	-	-	-	-			
Submandibular gland		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Sublingual gland		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Lymph node, submandibular		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Thyroid gland							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-					NE	NE	
Ultimobranchial rest	P	-	-	-	-	-											-	P	-	-	-			
Parathyroid gland		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Thymus		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Heart							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE	
Degeneration/fibrosis, myocardial, focal	-	-	-	±	-	±											-	±	-	-	-			
Trachea		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Lung							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE	
Accumulation, foam cell, alveolus	-	±	±	±	±	-											±	-	-	±	-			
Hemorrhage, focal	-	-	-	±	-	-											-	-	-	-	-			
Metaplasia, osseous, focal	-	-	-	-	±	-											-	-	-	-	-			
Mineralization, focal, arterial wall	-	-	-	±	-	±											-	-	-	-	-			
Bronchus		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Liver																								
Fatty change, hepatocyte, periportal	±	±	+	+	±		±	±	±	±	±	±	-	±	±	±	±	±	±	+	±	±	±	
Hypertrophy, hepatocyte, diffuse, with anisonucleosis	-	-	-	-	-		-	-	-	-	-	+	±	±	±	±	+	±	+	+	+	±	+	
Microgranuloma	-	-	±	-	-		-	±	-	-	±	±	±	±	±	±	±	±	±	±	+	±	±	
Necrosis, focal, subserosa	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	±	-	-	-	-	-	
Single cell necrosis	-	-	-	-	-		-	-	-	-	-	-	±	±	±	±	+	±	-	±	+	-	-	
Pancreas							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE	
Cellular infiltration, lymphocyte, interstitial	±	-	-	-	-												-	-	-	-	-			

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg) Animal No.	4-IBA 0					4-IBA 30					4-IBA 100					4-IBA 300/150							
		M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04	M04	M04	M04
		001	002	003	004	005	013	014	015	016	017	025	026	027	028	029	037	038	039	040	041	042	043	
Stomach		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	a	
Duodenum		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Jejunum		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Ileum		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Cecum		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Colon		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Rectum		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Lymph node, mesenteric		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Spleen																						NE	NE	
Deposit, pigment, brown		±	±	+	+	±	±	±	+	+	±	+	+	+	+	+	2+	+	+	2+	+			
Hematopoiesis, extramedullary		+	+	+	+	±	+	+	+	+	±	+	+	+	+	+	+	+	+	+	±			
Kidney							NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	NE	
Basophilic tubule, cortex		±	-	±	-	-											±	-	-	-	-			
Mineralization, medulla		-	-	-	±	-											-	-	±	-	-			
Urinary bladder		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	
Adrenal gland		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-	NE	NE	

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Findings	Group Dose(mg/kg)	4-IBA 0					4-IBA 30					4-IBA 100					4-IBA 300/150							
	Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M02 013	M02 014	M02 015	M02 016	M02 017	M03 025	M03 026	M03 027	M03 028	M03 029	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 043	
Testis																								
Atrophy, seminiferous tubule, focal bilateral		2+	-	-	-	-	-	±	-	-	-	-	-	-	-	-	2+	+	2+	+	2+	+	+	
Decrease, elongated spermatid, seminiferous tubule, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2+	2+	+	+	+	+	+	
Hyperplasia, Leydig cell, interstitial, bilateral		+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±	±	±	±	±	±	±	
Multinucleated giant cell, seminiferous tubule, bilateral		+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	±	±	-	
Epididymis																								
Cell debris, lumen, bilateral		2+	-	-	-	-	-	±	-	-	-	±	±	±	±	±	+	2+	2+	+	2+	2+	+	
Decrease, sperm, lumen bilateral		-	-	-	-	-	-	-	-	-	-	+	+	±	±	+	2+	2+	2+	2+	2+	2+	2+	
Granuloma, spermatic, caudal, bilateral/unilateral		-	-	-	-	-	-	-	-	-	-	2+	+	-	-	2+	2+	-	-	-	-	2+	-	
Prostate																								
Cellular infiltration, lymphocyte, interstitial		±	-	-	±	+	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	±	±	-	±	±		NE	NE
Seminal vesicle																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Coagulating gland																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Eyeball																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Harderian gland																								
Cellular infiltration, lymphocyte		±	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Sciatic nerve																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Skeletal muscle																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Femur																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE
Marrow, femur																								
		-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	-	-	-	-		NE	NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-2. Histopathological findings of male rats at the end of the recovery period,

Findings	Group Dose(mg/kg) Animal No.	4-IBA 0					4-IBA 100					4-IBA 300/150				
		M01 008	M01 009	M01 010	M01 011	M01 012	M03 032	M03 033	M03 034	M03 035	M03 036	M04 044	M04 045	M04 046	M04 047	M04 048
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Dilatation, Rathke's pouch																
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial rest																
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Degeneration/fibrosis, myocardial, focal																
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Accumulation, foam cell, alveolus																
Hemorrhage, focal																
Metaplasia, osseous, focal																
Mineralization, focal, arterial wall																
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Liver																
Fatty change, hepatocyte, periportal		±	±	+	±	-	-	±	±	-	±	-	-	-	-	-
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		-	-	-	-	-	-	-	-	±	-	+	+	±	±	±
Microgranuloma		±	±	-	±	±	-	-	-	-	-	-	-	-	-	-
Necrosis, focal, subserosa		-	-	-	-	-	-	-	-	-	-	-	-	±	-	-
Single cell necrosis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial																

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group Dose(mg/kg) Animal No.	4-IBA 0					4-IBA 100					4-IBA 300/150				
		M01 008	M01 009	M01 010	M01 011	M01 012	M03 032	M03 033	M03 034	M03 035	M03 036	M04 044	M04 045	M04 046	M04 047	M04 048
Stomach		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen																
Deposit, pigment, brown		+	+	2+	+	2+	+	+	2+	2+	2+	+	+	2+	+	+
Hematopoiesis, extramedullary		+	+	+	±	+	±	+	+	+	+	+	+	+	+	±
Kidney		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA					4-IBA				
	Dose(mg/kg)	0					100					300/150				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M03 032	M03 033	M03 034	M03 035	M03 036	M04 044	M04 045	M04 046	M04 047	M04 048
Testis																
Atrophy, seminiferous tubule, focal bilateral		-	-	-	-	-	-	-	-	-	-	+	+	2+	+	+
Decrease, elongated spermatid, seminiferous tubule, bilateral		-	-	-	-	-	-	-	-	-	-	+	+	2+	2+	2+
Hyperplasia, Leydig cell, interstitial, bilateral		-	-	-	-	-	-	-	-	-	-	±	±	±	±	±
Multinucleated giant cell, seminiferous tubule, bilateral		-	-	-	-	-	-	-	-	-	-	±	-	±	±	±
Epididymis																
Cell debris, lumen, bilateral		-	-	-	-	-	±	±	±	±	±	2+	+	2+	+	2+
Decrease, sperm, lumen bilateral		-	-	-	-	-	±	+	±	±	±	2+	2+	3+	2+	3+
Granuloma, spermatic, caudal, bilateral/unilateral		+	-	-	-	-	-	2+	-	2+	-	-	-	-	-	-
Prostate																
Cellular infiltration, lymphocyte, interstitial		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Seminal vesicle																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland																
Cellular infiltration, lymphocyte		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur																
		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period

[illegible]

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Findings	Group	4-IBA												4-IBA												4-IBA												4-IBA															
	Dose(mg/kg)	0												30												100												300/150															
	Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048				
	Fate	NP																TL	NP	NP									NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	D	D	D	NP	NP	D	NP	NP	
Liver		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Degeneration, vacuolar, hepatocyte																																																					
Fatty change, hepatocyte, periportal																																																					
Hematopoiesis, extramedullary																																																					
Hypertrophy, hepatocyte, diffuse, with anisonucleosis																																																					
Microgranuloma																																																					
Single cell necrosis																																																					
Pancreas		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	
Stomach		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	-	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Edema, lamina propria mucosa, forestomach																																																					
Erosion, mucosa, forestomach																																																					
Ulcer, mucosa, forestomach																																																					
Duodenum		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	
Jejunum		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy																																																					
Spleen		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Decrease, red pulp																																																					
Decrease, white pulp																																																					
Depos, pigment, brown																																																					
Hematopoiesis, extramedullary																																																					
Kidney		NE	NE	-	NE	NE	NE	-	NE	-	NE	-	-	NE	NE	-	-	NE	NE	NE	NE	NE	-	-	-	-	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Basophilic tubule, cortex																																																					
Degeneration, vacuolar, distal/ collecting tubule																																																					
Mineralization, C-M junction, focal																																																					
Necrosis, pan/la																																																					

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on day 5 of lactation; D, died; NP, not pregnant; TL, total litter loss

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

[illegible]

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on day 5 of lactation; D, died; NP, not pregnant; TL, total litter loss

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	4-IBA					4-IBA						
	Dose(mg/kg)	0					300/150						
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06	F06	F06
	Fate	049	050	051	052	053	059	060	061	062	063	064	068
Brain		-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular Atrophy		-	-	-	-	-	-	-	-	-	+	-	+
Thyroid gland		-	-	-	-	-	-	-	-	-	-	-	-
Parathyroid gland		-	-	M	-	-	-	-	-	M	-	-	-
Thymus Atrophy		-	-	-	-	-	-	-	-	-	3+	2+	3+
Heart Degeneration/fibrosis, myocardial, focal		-	-	-	-	-	±	-	-	-	-	±	-
Trachea		-	-	-	-	-	-	-	-	-	-	-	-
Lung Accumulation, foam cell, alveolus		-	-	-	-	-	±	±	-	-	-	-	+
Bronchus		-	-	-	-	-	-	-	-	-	-	-	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	4-IBA					4-IBA						
	Dose(mg/kg)	0					300/150						
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06	F06	F06
	Fate	049	050	051	052	053	059	060	061	062	063	064	068
							D		S		D	D	
Liver													
Degeneration, vacuolar, hepatocyte		-	-	-	-	-	±	-	-	-	±	+	2+
Fatty change, hepatocyte, periportal		-	±	-	±	-	-	+	±	±	-	+	-
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		-	-	-	-	-	2+	+	±	±	2+	2+	2+
Microgranuloma		-	-	±	-	±	-	-	±	-	+	-	-
Pancreas													
		-	-	-	-	-	-	-	-	-	-	-	-
Stomach													
Edema, lamina propria mucosa, forestomach		-	-	-	-	-	-	-	-	+	-	-	-
Erosion, mucosa, glandular stomach		-	-	-	-	-	-	±	-	-	-	-	-
Hyperplasia, squamous cell, forestomach		-	-	-	-	-	-	-	-	±	-	-	-
Duodenum													
		-	-	-	-	-	-	-	-	-	-	-	-
Jejunum													
		-	-	-	-	-	-	-	-	-	-	-	-
Ileum													
		-	-	-	-	-	-	-	-	-	-	-	-
Cecum													
		-	-	-	-	-	-	-	-	-	-	-	-
Colon													
		-	-	-	-	-	-	-	-	-	-	-	-
Rectum													
		-	-	-	-	-	-	-	-	-	-	-	-

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	4-IBA					4-IBA						
	Dose(mg/kg)	0					300/150						
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06	F06	F06	F06	F06
	Fate	049	050	051	052	053	059	060	061	062	063	064	068
							D				S	D	D
Lymph node, mesenteric													
Atrophy		-	-	-	-	-	-	-	-	-	+	+	2+
Spleen													
Decrease, red pulp		-	-	-	-	-	+	-	-	-	2+	2+	2+
Decrease, white pulp		-	-	-	-	-	±	-	-	-	+	+	2+
Deposit, pigment, brown		+	2+	+	+	2+	+	2+	2+	+	2+	2+	2+
Hematopoiesis, extramedullary		±	+	+	+	+	±	+	+	+	±	±	-
Kidney													
Basophilic tubule, cortex		-	-	-	-	-	-	-	-	-	-	-	-
Degeneration, vacuolar, distal/ collecting tubule		-	-	-	-	-	2+	+	±	±	+	2+	+
Mineralization, medulla		-	-	-	-	±	-	-	-	-	-	-	-
Necrosis, papilla		-	-	-	-	-	-	-	-	-	±	-	-
Urinary bladder													
		-	-	-	-	-	-	-	-	-	-	-	-
Adrenal gland													
Hypertrophy, cortical cell, zona fasciculata		-	-	-	-	-	-	-	-	-	+	+	+
Ovary													
Cyst, ovarian		-	-	-	±	-	-	-	-	-	-	-	-
Uterus													
		-	-	-	-	-	-	-	-	-	-	-	-
Vagina													
		-	-	-	-	-	-	-	-	-	-	-	-
Eyeball													
		-	-	-	-	-	-	-	-	-	-	-	-
Harderian gland													
		-	-	-	-	-	-	-	-	-	-	-	-
Sciatic nerve													
		-	-	-	-	-	-	-	-	-	-	-	-
Skeletal muscle													
		-	-	-	-	-	-	-	-	-	-	-	-
Femur													
		-	-	-	-	-	-	-	-	-	-	-	-
Marrow, femur													
Hematopoiesis, decreased		-	-	-	-	-	-	-	-	-	-	-	2+

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

P : Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA		
	Dose(mg/kg)	0					300/150		
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06
	Fate	054	055	056	057	058	065	066	067
Brain		NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular Atrophy		NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE
Thymus Atrophy		NE	NE	NE	NE	NE	NE	NE	NE
Heart Degeneration/fibrosis, myocardial, focal		NE	NE	NE	NE	NE	NE	NE	NE
Trachea		NE	NE	NE	NE	NE	NE	NE	NE
Lung Accumulation, foam cell, alveolus		NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA		
	Dose(mg/kg)	0					300/150		
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06
	Fate	054	055	056	057	058	065	066	067
Liver									
Degeneration, vacuolar, hepatocyte		-	-	-	-	-	-	-	-
Fatty change, hepatocyte, periportal		-	±	-	-	-	-	±	±
Hypertrophy, hepatocyte, diffuse, with anisonucleosis		-	-	-	-	-	-	-	-
Microgranuloma		-	±	-	±	-	-	-	-
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE
Stomach		NE	NE	NE	NE	NE	NE	NE	NE
Edema, lamina propria mucosa, forestomach									
Erosion, mucosa, glandular stomach									
Hyperplasia, squamous cell, forestomach									
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE
Atrophy									

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the end of the recovery period

Findings	Group	4-IBA					4-IBA		
	Dose(mg/kg)	0					300/150		
	Animal No.	F05	F05	F05	F05	F05	F06	F06	F06
	Fate	054	055	056	057	058	065	066	067
Spleen									
Decrease, red pulp		-	-	-	-	-	-	-	-
Decrease, white pulp		-	-	-	-	-	-	-	-
Deposit, pigment, brown		2+	2+	+	+	2+	2+	+	2+
Hematopoiesis, extramedullary		+	+	+	±	+	+	±	+
Kidney									
Basophilic tubule, cortex		-	-	-	-	-	-	-	±
Degeneration, vacuolar, distal/ collecting tubule		-	-	-	-	-	-	-	-
Mineralization, medulla		-	-	-	-	±	±	-	-
Necrosis, papilla		-	-	-	-	-	-	-	±
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE		NE	NE	NE	NE
Hypertrophy, cortical cell, zona fasciculata					-				
Ovary		NE	NE	NE	NE	NE	NE	NE	NE
Cyst, ovarian									
Uterus		NE	NE	NE	NE	NE	NE	NE	NE
Vagina		NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE
Femur		NE	NE	NE	NE	NE	NE	NE	NE
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE
Hematopoiesis, decreased									

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

P: Non-graded change NE: Not examined M: Missing A: Autolysis

Fate: blank, Subjected to autopsy on schedule; D, died; S, moribund sacrificed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle :corn oil)

Experiment 1 (Female: 12/01/01)									
Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F01001	D E D D D D E D D P E D D P	4/5-day	4.5	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F01002	D D P E D D D E D D D E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D D PL	1	
F01003	P E D D P E D D P E D D D E	4-day	4.0	D D P E D D P E D D D E D D	4-day	4.0	D PL	1	
F01004	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E E D D P E	4/5-day	4.3	D P P PL	1	
F01005	D D P E D D D E D D D E D D	4-day	4.0	D E D D D E D D P E D D D E	4-day	4.0	D D P PL	1	
F01006	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D P PL	1	
F01007	P E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D D E D D	4-day	4.0	P PL	1	
F01008	D D P E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F01009	D P E D D D E E D D D E D D	4/5-day	4.5	D D E D D D D E D D D P E D	5-day	5.0	D D PL	1	
F01010	D D D E D D D E D D D E D D	4-day	4.0	D E D D P E D D P E D D D E	4-day	4.0	D D P SP	1	
F01011	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1	
F01012	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
Mean			4.1			4.1		1.0	
S.D.			0.2			0.3		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 35-2. Results of observations about estrous cycle

4-IBA (30 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period			Stage	Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)		
F02013	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F02014	D D D E D D D E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F02015	E D D P E D D D E D D D E D	4-day	4.0	D D E D D P E D D D D D D D	irregular	4.0	D PL	1
F02016	E D D D E D D D E D D D E D	4-day	4.0	D D E D D D E E D D D E E D	5-day	5.0	D P E PL	1
F02017	D D E D D P E D D P E D D P	4-day	4.0	E D D D E D D P E D D D D E	4/5-day	4.3	PL	1
F02018	D D P E D D P E D D D E D D	4-day	4.0	D E D D D E D D D E D D D E	4-day	4.0	D D D SP	1
F02019	D D P E D D P E D D P E D D	4-day	4.0	P E D D D E D D P E D D P E	4-day	4.0	D D P SP	1
F02020	D D P E D D D E D D D E D D	4-day	4.0	D E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02021	D E D D P E D D D E E D D P	4/5-day	4.5	E D D D E D D D P E D D D E	4/5-day	4.3	D D P PL	1
F02022	D D D E D D D E D D D E D D	4-day	4.0	P E D D D P E D D D P E D D	5-day	5.0	D P PL	1
F02023	D E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1
F02024	P E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1
Mean			4.0			4.2		1.0
S.D.			0.1			0.4		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

4-IBA (100 mg/kg)

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F03025	D D E D D D E D D P E D D P	4-day	4.0	E D D D E D D P E D D D E D	4-day	4.0	D P PL	1	
F03026	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1	
F03027	E D D P E D D P E D D P E D	4-day	4.0	D D E D D P E D D D E D D D	4-day	4.0	PL	1	
F03028	D P E D D D E D D D E D D P	4-day	4.0	E D D D P E D D P E D D D E	4/5-day	4.3	D D D PL	1	
F03029	D D E D D D E E D D P E D D	4/5-day	4.5	D E E D D P E E D D D E D D	4/5-day	4.5	D P E PL	1	
F03030	D P E E D D D E E D D D E E	5-day	5.0	D D D D E D D P E E D D D P	5-day	5.0	PL	1	
F03031	D D P E D D P E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
F03032	D E D D P E D D P E D D D E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	D PL	1	
F03033	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D D E	4-day	4.0	D D P PL	1	
F03034	D P E D D D P E D D D P E D	5-day	5.0	D D D D E D D D D E D D D P	5-day	5.0	PL	1	
F03035	D D E D D D E D D P E D D D	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F03036	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1	
Mean			4.2			4.2		1.0	
S.D.			0.4			0.4		0.0	
(N)			(12)			(12)		(12)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

4-IBA (300/150 mg/kg)

Animal no.	Pre-mating period						Mating period		Times of vaginal estrus observed
	Pre-treatment period			Treatment period			Stage		
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)			
F04037	E D D P E D D P E D D D E D	4-day	4.0	D D E D D D D E D D D P E D	5-day	5.0	D P PL	1	
F04038	E D D P E D D D E D D P E D	4-day	4.0	D D E D D P E D D D E D D D	4-day	4.0	PL	1	
F04039	D D P E D D P E D D P E D D	4-day	4.0	P E D D D P E D D D E D D P	4/5-day	4.5	PL	1	
F04040	P E D D D P E D D D P E D D	5-day	5.0	D P E D D D E E D D D E D D	4/5-day	4.5	D PL	1	
F04041	E D D D D E D D D E D D D P	4/5-day	4.5	E D D D E D D D E D D D E D	4-day	4.0	D	Died on day 17 of treatment Died on day 14 of treatment	
F04042	D E D D P E D D P E D D D E	4-day	4.0	D D D P E D D D E D D D					
F04043	D P E D D P E D D P E D D D	4-day	4.0	E D D D P E D D P E D D P E	4/5-day	4.3	PL	1	
F04044	P E D D P E D D P E E D D D	4/5-day	4.5	E D D D E E D D P E D D P E	4/5-day	4.3	D D PL	1	
F04045	D P E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D D E D	4-day	4.0	D P PL	1	
F04046	D P E D D D E D D D E D D P	4-day	4.0	E D D D D E D D D D E D D D	5-day	5.0	D PL	1	
F04047	D D P E D D P E D D P E D D	4-day	4.0	D E D D D D D D D D P E D D	irregular	10.0	D PL	1	
F04048	D D D E D D P E D D P E D D	4-day	4.0	D E D D D D D D D D D D D D	uncycle		PL	1	
Mean			4.2			5.0		1.0	
S.D.			0.3			1.8		0.0	
(N)			(12)			(10)		(10)	

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug; SP, sperm positive

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: corn oil)				
Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	—	3
M01002	F01002	+	+	4
M01003	F01003	+	+	2
M01004	F01004	+	+	4
M01005	F01005	+	+	4
M01006	F01006	+	+	4
M01007	F01007	+	+	2
M01008	F01008	+	+	4
M01009	F01009	+	+	3
M01010	F01010	+	+	4
M01011	F01011	+	+	1
M01012	F01012	+	+	3
Total		+: 12, -: 0	+: 11, -: 1	
Mean				3.2
S.D.				1.0
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 36-2. Results of observations about reproductive performance

4-IBA (30 mg/kg)				
Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	4
M02014	F02014	+	+	4
M02015	F02015	+	+	2
M02016	F02016	+	+	4
M02017	F02017	+	+	1
M02018	F02018	+	—	4
M02019	F02019	+	—	4
M02020	F02020	+	+	4
M02021	F02021	+	+	4
M02022	F02022	+	+	3
M02023	F02023	+	+	2
M02024	F02024	+	+	2
Total		+: 12, -: 0	+: 10, -: 2	
Mean				3.2
S.D.				1.1
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

4-IBA (100 mg/kg)				
Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	—	3
M03026	F03026	+	—	3
M03027	F03027	+	—	1
M03028	F03028	+	—	4
M03029	F03029	+	—	4
M03030	F03030	+	—	1
M03031	F03031	+	—	4
M03032	F03032	+	—	2
M03033	F03033	+	—	4
M03034	F03034	+	—	1
M03035	F03035	+	—	3
M03036	F03036	+	—	4
Total		+: 12, -: 0	+: 0, -: 12	
Mean				2.8
S.D.				1.3
(N)				(12)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 36-4. Results of observations about reproductive performance

4-IBA (300/150 mg/kg)				
Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	—	3
M04038	F04038	+	—	1
M04039	F04039	+	—	1
M04040	F04040	+	—	2
M04041	F04041	+	Died	
M04043	F04043	+	—	1
M04044	F04044	+	—	3
M04045	F04045	+	—	3
M04046	F04046	+	—	2
M04047	F04047	+	—	2
M04048	F04048	+	—	1
Total		+: 11, -: 0	+: 0, -: 10	
Mean				1.9
S.D.				0.9
(N)				(10)

+, confirmed

-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 37-1. Observation of offspring (F₁)

Control (vehicle: corn oil)																			
Dam No.	Gestation length (days)	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring			External abnormalities (Number)		
						Number of offspring	Live			Sex ratio				Dead offspring	4 days	Sex ratio		Viability index (%)	
							Male	Female	Total										
F01001	Not pregnant																		
F01002	22	15	15	100.0	+	15	9	6	15	0.60	0	100.0	100.0	100.0	9	6	0.60	100.0	0
F01003	22	17	16	94.1	+	15	7	8	15	0.47	0	93.8	93.8	100.0	7	7	0.50	93.3	0
F01004	22	17	17	100.0	+	17	7	10	17	0.41	0	100.0	100.0	100.0	7	10	0.41	100.0	0
F01005	22	17	17	100.0	+	17	10	7	17	0.59	0	100.0	100.0	100.0	10	6	0.63	94.1	0
F01006	22	11	11	100.0	+	10	5	5	10	0.50	0	90.9	90.9	100.0	5	5	0.50	100.0	0
F01007	22	18	17	94.4	+	16	7	8	15	0.47	1	94.1	88.2	93.8	7	8	0.47	100.0	0
F01008	22	17	7	41.2	+	7	3	4	7	0.43	0	100.0	100.0	100.0	3	4	0.43	100.0	0
F01009	22	17	17	100.0	+	16	7	8	15	0.47	1	94.1	88.2	93.8	7	8	0.47	100.0	0
F01010	22	18	17	94.4	+	16	10	6	16	0.63	0	94.1	94.1	100.0	10	6	0.63	100.0	0
F01011	22	16	16	100.0	+	14	8	6	14	0.57	0	87.5	87.5	100.0	7	6	0.54	92.9	0
F01012	22	18	17	94.4	+	15	10	5	15	0.67	0	88.2	88.2	100.0	10	5	0.67	100.0	0
Number of dams	11	11	11	11	11 ^{a)}	11			11	11	11	11	11	11			11	11	11
Total		181	167			158	83	73	156		2				82	71			0
Mean	22.0	16.5	15.2	92.6		14.4	7.5	6.6	14.2	0.53	0.2	94.8	93.7	98.9	7.5	6.5	0.53	98.2	
S.D.	0.0	2.0	3.3	17.3		3.1	2.2	1.7	3.0	0.09	0.4	4.7	5.4	2.5	2.2	1.7	0.09	3.1	
%					100.0														

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 37-2. Observation of offspring (F₁)

4-IBA 30 mg/kg																			
Dam No.	Gestation length	Number of corpora lutea	Number of implantation scars	Implantation index (%)	Delivery index (dams) (%)	Number of offspring at birth					Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring				External abnormalities ^{b)} (Number)	
						Number of offspring	Live			Sex ratio				Dead offspring	4 days		Sex ratio		Viability index (%)
							Male	Female	Total						Male	Female			
	(days)															Male	Female		
F02013	22	14	14	100.0	+	12	4	8	12	0.33	0	85.7	85.7	100.0	4	8	0.33	100.0	0
F02014	22	15	15	100.0	+	13	7	6	13	0.54	0	86.7	86.7	100.0	6	5	0.55	84.6	0
F02015	21	19	19	100.0	+	18	9	9	18	0.50	0	94.7	94.7	100.0	9	9	0.50	100.0	0
F02016	21	16	14	87.5	+	11	8	3	11	0.73	0	78.6	78.6	100.0	8	3	0.73	100.0	0
F02017	23	16	16	100.0	-	6	0	0	0	C)	6	37.5	0.0	0.0	C)				
F02018	Not pregnant																		
F02019	Not pregnant																		
F02020	22	13	13	100.0	+	12	8	3	11	0.73	1	92.3	84.6	91.7	8	3	0.73	100.0	0
F02021	22	15	14	93.3	+	14	6	8	14	0.43	0	100.0	100.0	100.0	5	8	0.38	92.9	0
F02022	22	16	16	100.0	+	15	8	7	15	0.53	0	93.8	93.8	100.0	8	7	0.53	100.0	0
F02023	21	15	15	100.0	+	15	6	8	14	0.43	1	100.0	93.3	93.3	6	8	0.43	100.0	0
F02024	22	14	13	92.9	+	13	10	3	13	0.77	0	100.0	100.0	100.0	10	3	0.77	100.0	0
Number of dams	10	10	10	10	9 ^{a)}	10			10	9	10	10	10	10			9	9	9
Total		153	149			129	66	55	121		8				64	54			0
Mean	21.8	15.3	14.9	97.4		12.9	6.6	5.5	12.1	0.55	0.8	86.9	81.7	88.5	7.1	6.0	0.55	97.5	
S.D.	0.6	1.6	1.8	4.5		3.1	2.9	3.0	4.7	0.16	1.9	18.7	29.5	31.3	2.0	2.5	0.16	5.4	
%					90.0														
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	AW	AW	AW	AW	TT	TT	TT	TT	TT

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

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

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

c): Total litter loss on the lactation day 0

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 38-1. Body weights of offspring (F₁) before weaning

Control (vehicle: corn oil)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01002	6.3	(9)	10.3	(9)	5.7	(6)	9.5	(6)
F01003	6.3	(7)	9.6	(7)	6.4	(8)	9.8	(7)
F01004	6.5	(7)	10.3	(7)	6.2	(10)	9.4	(10)
F01005	5.6	(10)	8.2	(10)	5.0	(7)	8.0	(6)
F01006	6.9	(5)	12.1	(5)	6.4	(5)	11.7	(5)
F01007	6.7	(7)	10.5	(7)	6.4	(8)	9.8	(8)
F01008	7.5	(3)	14.3	(3)	7.1	(4)	13.6	(4)
F01009	6.2	(7)	9.4	(7)	6.3	(8)	9.7	(8)
F01010	6.2	(10)	10.1	(10)	6.1	(6)	10.0	(6)
F01011	5.9	(8)	11.4	(7)	6.0	(6)	10.2	(6)
F01012	6.5	(10)	8.8	(10)	6.2	(5)	8.7	(5)
Number of dams	11		11		11		11	
Mean	6.4		10.5		6.2		10.0	
S.D.	0.5		1.7		0.5		1.5	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde by oral administration in rats

Appendix 38-2. Body weights of offspring (F₁) before weaning

4-IBA 30 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	7.2	(4)	10.0	(4)	6.4	(8)	9.6	(8)
F02014	6.5	(7)	11.8	(6)	6.1	(6)	10.9	(5)
F02015	5.3	(9)	6.8	(9)	5.0	(9)	6.6	(9)
F02016	5.1	(8)	7.7	(8)	4.8	(3)	6.9	(3)
F02017	Total litter loss							
F02020	6.6	(8)	12.0	(8)	6.0	(3)	11.3	(3)
F02021	6.0	(6)	9.9	(5)	5.7	(8)	9.6	(8)
F02022	5.1	(8)	8.1	(8)	5.1	(7)	8.4	(7)
F02023	5.7	(6)	9.0	(6)	5.3	(8)	9.0	(8)
F02024	6.0	(10)	9.6	(10)	5.9	(3)	9.6	(3)
Number of dams	9		9		9		9	
Mean	5.9		9.4		5.6		9.1	
S.D.	0.7		1.8		0.6		1.6	
Significance	NS		NS		*		NS	
Statistical method	TT		TT		TT		TT	

Each value shows mean per dam (g).

Figures in parentheses indicate number of offspring.

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

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde
by oral administration in rats

Appendix 39-1. General conditions in offspring (F₁) before weaning

Control (vehicle: corn oil)						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F01001	Not pregnant					
F01002	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01003	Number of offspring	15	15	15	14	14
	General appearance, No abnormality	15	15	14	14	14
	General appearance, Death	0	0	1	0	0
F01004	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F01005	Number of offspring	17	17	17	16	16
	General appearance, No abnormality	17	17	16	16	16
	General appearance, Death	0	0	1	0	0
F01006	Number of offspring	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10
F01007	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01008	Number of offspring	7	7	7	7	7
	General appearance, No abnormality	7	7	7	7	7
F01009	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01010	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01011	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	13	13	13	13
	General appearance, Death	0	1	0	0	0
F01012	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
	Number of offspring	156	156	155	153	153
	General appearance, No abnormality	156	155	153	153	153
	General appearance, Death		1	2		

Combined repeat dose and reproductive/developmental toxicity screening test of 4-isopropylbenzaldehyde
by oral administration in rats

Appendix 39-2. General conditions in offspring (F₁) before weaning

4-IBA 30 mg/kg						
Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F02014	Number of offspring	13	13	11	11	11
	General appearance, No abnormality	13	11	11	11	11
	General appearance, Death	0	2	0	0	0
F02015	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F02016	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F02017	Total litter loss on the lactation day 0					
F02020	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
F02021	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	13	13	13	13
	General appearance, Death	0	1	0	0	0
F02022	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02023	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02024	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
	Number of offspring	121	121	118	118	118
	General appearance, No abnormality	121	118	118	118	118
	General appearance, Death		3			

信頼性保証書

表題 4-isopropylbenzaldehyde のラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号 R-12-002

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2012 年 9 月 6 日	2012 年 9 月 6 日
試験計画書変更書		
R-12-002-No.1	2012 年 10 月 12 日	2012 年 10 月 12 日
R-12-002-No.2、No.3	2012 年 11 月 5 日	2012 年 11 月 5 日
R-12-002-No.4	2012 年 11 月 16 日	2012 年 11 月 16 日
R-12-002-No.5	2013 年 1 月 9 日	2013 年 1 月 9 日
R-12-002-No.6	2013 年 3 月 21 日	2013 年 3 月 21 日
R-12-002-No.7	2013 年 4 月 1 日	2013 年 4 月 1 日
動物の受入れおよび検疫	2012 年 9 月 10 日	2012 年 9 月 11 日
媒体中の安定性(安定性試験開始日)	2012 年 9 月 11 日	2012 年 9 月 11 日
群分け、検体調製および含量試験	2012 年 9 月 24 日	2012 年 9 月 24 日
体重測定、給餌量測定、投与および一般状態の観察	2012 年 9 月 25 日	2012 年 9 月 25 日
性周期観察	2012 年 9 月 26 日	2012 年 9 月 26 日
詳細な症状観察	2012 年 10 月 2 日	2012 年 10 月 2 日
交尾確認	2012 年 10 月 10 日	2012 年 10 月 10 日
尿検査	2012 年 10 月 31 日、 2012 年 11 月 1 日	2012 年 11 月 1 日
分娩状態および出生児の観察	2012 年 11 月 1 日	2012 年 11 月 1 日
機能検査	2012 年 11 月 2、5 日	2012 年 11 月 5 日
出生児剖検、血液学検査、血液生化学検査、雄動物剖検、器官重量測定および固定	2012 年 11 月 6 日	2012 年 11 月 6 日
病理組織学的検査(標本作製:切り出し)	2012 年 11 月 12 日	2012 年 11 月 12 日
報告書草案および生データ	2013 年 3 月 26～29 日、 2013 年 4 月 1～5、8～12 日	2013 年 4 月 12 日
最終報告書	2014 年 3 月 12、13 日	2014 年 3 月 13 日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成 23 年 3 月 31 日、薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、環企発第 110331010 号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014 年 3 月 13 日

一般財団法人食品薬品安全センター 秦野研究所
信頼性保証部門責任者 [Redacted]