R-1114

原本

最　終　報　告　書

リアクティブ　ブラック-5 のラットを用いた
経口投与による反復投与毒性･生殖発生毒性併合試験

試験番号：R-1114

試験期間：2013 年 8 月 5 日-2014 年 3 月 24 日

試験施設
株式会社ボゾリサーチセンター　御殿場研究所
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1. GLP 陳述書

試験番号　　：　R-1114

試験表題　　：　リアクティブ　ブラック-5 のラットを用いた
経口投与による反復投与毒性・生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施したものであります。

- 「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：薬食発 0331 第 8 号、平成 23・03・29 製局第 6 号、
環保企発第 110331010 号）

[redacted]　　2014年 3 月 24日 [redacted]

試験責任者
株式会社ボゾリサーチセンター　御殿場研究所

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3. 試験実施概要

3.1 試験番号

R-1114

3.2 試験表題

リアクティブ ブラック-5 のラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験

(Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats)

3.3 試験目的

本試験は、動物に被験物質を一定期間反復投与したときに現れる被験物質の一般毒性及び生殖発生毒性を明らかにすることを目的とした。

3.4 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

〒100-8916 東京都千代田区霞が関 1-2-2

3.5 試験受託者

株式会社ボゾリサーチセンター

〒151-0065 東京都渋谷区大山町 36-7

3.6 試験実施施設

株式会社ボゾリサーチセンター 御殿場研究所

〒412-0039 静岡県御殿場市かまど 1284

3.7 被験物質

製造者	:	Sigma-Aldrich Co.
名称	:	リアクティブ ブラック-5
英名	:	C.I. Reactive Black-5
CAS 番号	:	17095-24-8
官報公示整理番号	:	5-3012
入手日	:	2013 年 5 月 9 日

3.8 試験日程

試験開始日	:	2013 年 8 月 5 日
被験物質出庫日	:	2013 年 8 月 20 日

動物入荷日　　：　2013 年　8 月　7 日
実験開始日（投与開始日）
　　：　2013 年　8 月 27 日
交配開始日　　：　2013 年　9 月 10 日
分娩開始日　　：　2013 年 10 月　2 日
母動物剖検開始日　：　2013 年 10 月　7 日
投与終了剖検日　：　2013 年 10 月　8 日　（雄及び非交配群）
回復開始日　　：　2013 年 10 月　8 日
回復終了剖検日　：　2013 年 10 月 22 日
動物試験終了日　：　2013 年 10 月 22 日
実験終了日（病理組織学検査終了日）
　　：　2014 年　1 月　7 日
試験終了日　　：　2014 年　3 月 24 日

3.9　試験責任者

株式会社ボゾリサーチセンター　御殿場研究所　研究部

[redacted]

3.10　試験担当者

試験主担当者　　：
被験物質保存責任者：

臨床検査責任者　：
化学分析責任者　：
病理検査責任者　：
統計解析責任者　：

[redacted]

3.11　試験成績の信頼性に影響を及ぼしたと思われる環境要因

本試験に関し､試験成績の信頼性に影響を及ぼしたと思われる環境要因はなかった。

3.12　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

1) 試験計画書において膣垢採取は、非交配群及び交尾不成立動物について、剖検 6 日前から剖検日まで検査することになっていたが、交尾不成立動物番号 2112 の膣垢採取（2013 年 10 月 13 日~10 月 19 日）が漏れてしまった。しかし、交尾能力に被験物質の影響がなかったことから､試験成績に影響は及ぼさないと判断した。

2) 病理組織学検査の標本作製において、上皮小体（両側）の欠落が、対照群の雌1例（No.1106）にみられた。しかし本動物は、鏡検対象動物ではない為、病理評価上に影響は及ぼさなかった。

3.13 資料の保存

株式会社ボゾリサーチセンターの保存方法に従い、試験計画書原本（試験計画書変更書を含む）、記録文書、生データ、報告書類（最終報告書は原本）及び標本（被験物質保存サンプルを含む）は株式会社ボゾリサーチセンター御殿場研究所の資料保存施設に最終報告書提出後5年間保存する。期間終了後の保存については、厚生労働省医薬食品局　審査管理課　化学物質安全対策室と株式会社ボゾリサーチセンター間で協議し、その処置を決定する。ただし、長期保存に耐えられない生体試料（尿、血漿、血清）及び腟垢標本については、試験終了までに廃棄した。また、死産児、死亡児及び生後4日出生児については、出生率及び生後4日生存率に被験物質投与の影響が認められなかったため、試験終了までに廃棄した。

3.14 試験責任者の記名・なつ印

[redacted]　2014 年 3 月 24 日 [redacted]

4. 要約

リアクティブ　ブラック-5 を注射用水で溶解し、40、200 及び 1000 mg/kg の投与量で Sprague-Dawley 系 SPF ラットの雄（12 匹/群）には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌（12 匹/群）には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（39~47 日間、全児死産動物を含む）、非交配群（対照群及び 1000 mg/kg 投与群：10 匹/群）には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、対照群及び 1000 mg/kg 投与群の一部の動物（雄及び非交配群の各群 5 匹）については、42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、対照群には媒体である注射用水を投与した。

4.1　反復投与毒性

各被験物質投与群で被験物質の色調を反映したと考えられる着色糞（濃青色）、着色尿（淡紫色）、全身皮膚と精巣の青色化、腎臓と肝臓の黒色化がみられた。1000 mg/kg 投与群において、腺胃粘膜の過形成及び境界縁の扁平上皮細胞過形成が雄と交配群雌及び非交配群で、大腸粘膜のびまん性過形成が直腸では雄と交配群雌及び非交配群に、盲腸では雄及び非交配群に、結腸では雄にみられ、膀胱で移行上皮のびまん性過形成が雄、交配群雌及び非交配群に認められた。また、200 mg/kg 以上の投与群の雄で腎臓の相対重量の高値と、抗 α2u グロブリン抗体による免疫染色で陽性を示す尿細管の好酸性小体の増加、1000 mg/kg 投与群の雄及び非交配群でナトリウムの尿中排泄量が高値、雄で血中カリウム及び塩素の低値、非交配群で塩素の低値と腎臓の絶対重量の高値、交配群雌で尿素窒素の高値が認められた。更に、1000 mg/kg 投与群の雄でプロトロンビン時間の延長、非交配群でフィブリノーゲン量の低値、肝臓の相対重量の高値もみられた。これら変化は回復期間終了時に消失あるいは軽減した。また、1000 mg/kg 投与群の雄で投与終了時に総胆汁酸の高値が認められたが、回復終了時にも引き続いてみられ、回復性は明らかでなかった。

4.2　生殖発生毒性

雌雄動物及び児動物に被験物質投与の影響は認められなかった。

これらの結果から、本被験物質の反復投与毒性に対する無影響量及び無毒性量は雄で 40 mg/kg、雌で 200 mg/kg と判断した。また、雌雄親動物の生殖能力に対する無影響量及び無毒性量は雌雄で 1000 mg/kg、児動物おける無影響量及び無毒性量は 1000 mg/kg と判断した。

5. 緒言

厚生労働省　医薬食品局　審査管理課　化学物質安全対策室の委託により、リアクティブ　ブラック-5 のラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験を実施したので、その成績を報告する。

本試験は以下の基準を遵守し、ガイドライン等に準拠して、株式会社ボゾリサーチセンターで実施した。

1) GLP

- 「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：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

2) 毒性試験ガイドライン

- 「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：薬食発 0331 第 7 号、平成 23･03･29 製局第 5 号、環保企発第 110331009 号）

3) 動物の福祉

- 「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）
- 「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）
- 「動物実験の適正な実施に向けたガイドライン」
  （日本学術会議 平成 18 年 6 月 1 日）

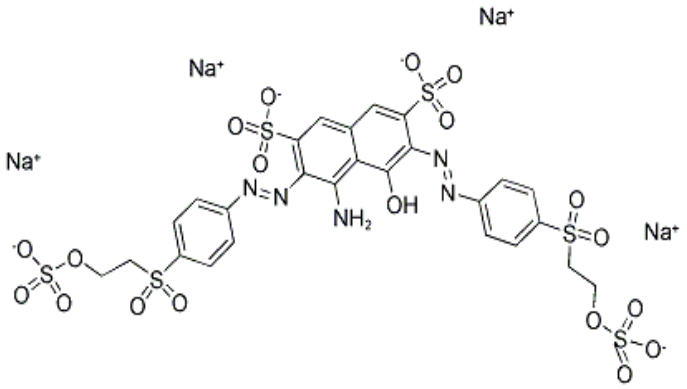
本試験は動物実験委員会の承認を受けて実施した（承認番号：G130202）。

6. 試験材料及び方法

6.1 被験物質及び媒体

6.1.1 被験物質

リアクティブ ブラック-5 は[redacted]から以下の情報とともに購入した。また、試験開始前に赤外吸収スペクトルの測定により特性が確認されている（試験番号：A-2543、添付資料 1）。

製造者	:	[redacted]
名称	:	リアクティブ　ブラック-5
英名	:	C.I. Reactive Black-5
化学名	:	テトラナトリウム= 4-アミノ-5-ヒドロキシ-3, 6-ビス｛4-[2-（オキシドスルホニルオキシ）エチルスルホニル]フェニルアゾ｝-2, 7-ナフタレンジスルホナート
CAS 番号	:	17095-24-8
官報公示整理番号	:	5-3012
構造式又は示性式	:	
分子式	:	$C_{26}H_{21}N_5Na_4O_{19}S_6$
分子量	:	991.82
性状	:	暗紫色の粉末
ロット番号	:	15112DDV
色素含量	:	55%（秤量時の換算係数 1.818）
融点	:	180°C（1.013 hPa）
比重	:	1.21 g/cm^3（20°C）
溶解度	:	550 g/L（20°C）
n-オクタノール/水分配係数	:	log Pow: <-4.34（20°C）
引火点	:	>180°C
銅	:	0.7 ppm

鉛	:	24 ppm
カドミウム	:	検出せず（定量下限 0.5 ppm）
総水銀	:	検出せず（定量下限 0.1 ppm）
スズ	:	検出せず（定量下限 1 ppm）
アンチモン	:	検出せず（定量下限 5 ppm）
ビスマス	:	検出せず（定量下限 5 ppm）
入手量	:	2000 g（関連試験を含む）
保存条件	:	気密、冷所
保存方法	:	気密容器に入れ冷蔵庫内（許容値：1~10°C、実測値：3~8°C）に保存。
保存場所	:	御殿場研究所被験物質保存室、第 3 研究棟 2 階被験物質調製室及び生化学部標準物質保存場所
取扱い上の注意	:	作業場の換気を十分に行い、マスク、保護眼鏡、保護手袋等の適切な保護具を着用し、直接の接触を防いだ。取り扱い後は、手、顔等を良く洗い、うがいを行った。
安定性	:	投与期間終了後に株式会社ボゾリサーチセンター御殿場研究所において、残余被験物質の赤外吸収スペクトルを確認した結果、実験実施前に確認した参照スペクトルとほぼ同様であり安定性に問題はなかった（添付資料 2）。
残余被験物質の処理	:	被験物質 1 g を保存試料として御殿場研究所の資料保存施設に保存した。動物試験及び分析終了後の残量は全て焼却処分した。

6.1.2 媒体

名称	:	注射用水	
規格	:	日本薬局方	
製造者	:	株式会社大塚製薬工場	
ロット番号及び有効期限			
		ロット番号	有効期限
	:	2J79	2017 年 10 月
		2K90	2017 年 11 月
		2L88	2017 年 12 月
保存方法	:	室温	
保存場所	:	御殿場研究所第 3 研究棟 2 階被験物質調製室	

なお、媒体は、本試験に先立って実施したリアクティブ　ブラック-5 の IR を用いた特性試験並びに吸光光度法を用いた被験液（媒体：注射用水）中濃度測定法バリデ

ーション及び安定性試験（試験番号：A-2543）[1]において、注射用水中での被験物質の安定性に良好な結果が得られていることから、注射用水を選択した。

6.2　投与液の調製及び保存方法

6.2.1　対照群投与液の採取

被験液調製当日の被験物質を取り扱う前に、対照群投与液として必要量の媒体を褐色ガラス瓶に貼付したラベルを確認しながら分注した。

6.2.2　被験液の調製

被験液の調製は先ず、濃度ごとに必要量の被験物質を秤取(換算係数 1.818 を乗じて秤量)した。次に、ビーカーに適量（規定量の 7~9 割程度）の注射用水を入れ、スターラーで撹拌しながら被験物質を少量ずつ加え、超音波処理を施した。その後、メスシリンダーに移し、ビーカーを少量の注射用水で数回洗い、その液もメスシリンダーに加え規定量にメスアップし、8、40 及び 200 mg/mL 液（低、中及び高用量群投与液）とした。調製は最大 7 日分を一括して行った。残液はポリ瓶に回収又はペーパータオル等に吸着させて焼却処分した。

6.2.3　投与液の保存

投与液は、褐色ガラス瓶に入れて冷所（冷蔵庫内、許容値：1~10°C、実測値：4~7°C）に保存し、安定性の確認された範囲内で投与に使用した。

6.2.4　被験液の安定性

本被験物質の 1 及び 200 mg/mL 液は、褐色ガラス瓶に入れ冷所（冷蔵庫内、許容値：1~10°C）で 8 日間、その後室温で 24 時間安定であることが株式会社ボゾリサーチセンターで確認されている（試験番号：A-2543、添付資料 3）[1]。

6.2.5　被験液の濃度確認

初回投与及び投与 6 週の投与に使用する各濃度の被験液(各 10 mL 採取)について、株式会社ボゾリサーチセンター御殿場研究所で吸光光度法により濃度確認を実施した。なお、初回投与に使用する被験液については、投与開始前に確認を行った。その結果、各濃度液における表示値に対する被験物質の割合は 101.0~105.0%であり、いずれも許容範囲内（濃度：表示値に対する割合；100.0±10%）であり（添付資料 4、5）、被験液の調製に問題はなかった。なお、吸光光度法バリデーションは株式会社ボゾリサーチセンター御殿場研究所（試験番号：A-2543）[1]で実施された。分析法の概略を以下に示した。

なお、初回投与に使用する被験液の濃度確認直前（2013 年 8 月 23 日）に落雷による停電が発生し、自記分光光度計 U-3200 の電源が落ちた。しかし、自記分光光度計はゼロ補正のみ実施した状態であり、再起動後に使用時点検項目に問題がないことを

確認した後、再びゼロ補正から実施し、濃度測定を実施したため試験結果に影響を及ぼさなかった。

[測定対象物質]
リアクティブ　ブラック-5
[標準物質]
被験物質の一部を標準物質として使用した。

名称	:	リアクティブ　ブラック-5
ロット番号	:	15112DDV
色素含量	:	55%（秤量時の換算係数：1.818）
保存条件	:	気密、冷所（冷蔵庫内、許容値：1~10°C、実測値：3~8°C）
保存場所	:	御殿場研究所被験物質保存室、第 3 研究棟 2 階被験物質調製室及び生化学部標準物質保存場所

[測定実測試料の調製]
被験液の任意の場所から n=3 で採取し、以下に示すように測定実測試料を用時に調製した。

被験液濃度 (mg/mL)	1 次希釈		2 次希釈		希釈率
	採取量 (mL)	定容量 (mL)	1 次希釈液 採取量 (mL)	定容量 (mL)	
8	0.5	20	1	20	800
40	0.5	50	0.5	20	4000
200	0.5	100	0.5	50	20000

溶媒：注射用水

[自記分光光度計]

自記分光光度計	:	U-3200（株式会社日立製作所）

[吸光光度計測定条件]

測定波長	:	600 nm
対照試料	:	注射用水
セル	:	1 cm 石英セル
ゼロ補正	:	測定実施前に、対照セル及びサンプルセルに対照試料を入れ、ゼロ補正を実施した。

6.3　試験動物種及び系統の選択理由

毒性試験法ガイドラインによりげっ歯類を用いた試験が必要とされていることからラットを選択した。また、この試験に使用された系統のラットは一般毒性試験、生殖発生毒性試験に広く用いられ、かつ、その特性がよく知られており、背景資料が豊富

であることから選択した。

6.4　試験動物

Sprague-Dawley 系 SPF ラット〔Crl:CD(SD)、日本チャールス・リバー株式会社、厚木飼育センター〕の雄 62 匹及び雌 83 匹をそれぞれ 8 週齢で入手[注]し、入荷日を馴化 1 日と起算して、3 日間の検疫期間を含む 20 日間の馴化飼育を行った。その間に一般状態の観察（1 回/日）、体重測定（馴化 1、3、8、13 及び 20 日の 5 回）、詳細な一般状態の観察（群分け 4 日前の馴化 16 日に 1 回）を行った。更に、雄は馴化終了日に陰嚢内の精巣の触診及び陰茎亀頭の観察を行った。また、雌は腟垢を検疫期間終了後群分け日まで採取して性周期（検疫期間終了後 14 日間）を調べた。その結果、以下の異常がみられた。

耳標番号	雄の異常所見	耳標番号	雌の異常所見
468	精巣の小型化	489、490、504、519、540	性周期の異常
413	頬部の腫脹	505	胸部から腹部の脱毛
427	眼瞼反射不良	−	−

上記の異常例を除き、検疫・馴化期間中の一般状態、詳細な一般状態、体重推移、精巣の触診結果及び性周期に異常がなく、性成熟に達した陰茎亀頭であり、健康と思われる雄 48 匹と雌 68 匹を選択し、それぞれ 10 週齢で投与に使用した。投与に供した動物の投与開始時（10 週齢）の体重範囲は雄で 383~465 g（平均体重：415 g）、雌で 230~293 g（平均体重：253 g）であり、雌雄それぞれ平均体重の±20%以内であった。

なお、動物は検疫・馴化期間中の体重増加量（入荷日~群分け時）により選別後、群分け当日（投与開始の前日）の体重に基づいて、非交配群も含め各群の平均体重ができるだけ均等となるよう各群に割付けた。個体の割付けはコンピュータを用いたブロック配置法及び無作為抽出法の組み合わせ（ブロック配置法で必要な群を構成し、試験群及び群内の個体番号を無作為に割当てた）により行った。供試個体の選択条件を満たして余剰となった雌は、無処置動物として継続飼育した。残りの雌雄動物は群分け当日に試験から除外し､有効利用を目的として動物管理責任者に移管した｡なお、使用しなかった無処置動物は、交配期間終了日に試験から除外し、有効利用を目的として動物管理責任者に移管した。

注：　試験計画書に従い、動物発注数は雄 60 匹及び雌 80 匹であったが、実際には雄 62 匹及び雌 83 匹が納入された。

6.5　飼育条件

動物は、温度 23±3°C（実測値：22~24°C）、相対湿度 50±20%（実測値：40~59%）、換気回数 12~17 回/時間、照明 12 時間/日（07:00~19:00）の動物飼育室（飼育室番号：3111 号室）でブラケット式金属製網ケージ（W254×D350×H170 mm：リードエンジニアリング株式会社）に個別に収容した。なお、交配中は雌雄各 1 匹収容した。また、

妊娠 17 日から授乳 4 日までは、床敷（ホワイトフレーク：日本チャールス・リバー株式会社、ロット番号：2013-2）を入れたプラスチック製エコンケージ（W340×D400×H185 mm：日本クレア株式会社）に 1 腹単位で収容した。

飼料は、NMF 固形（放射線滅菌、オリエンタル酵母工業株式会社、ロット番号：130619、130718 及び 130822）をステンレス製給餌器により自由に摂取させた。

飲料水は、御殿場市営水道水を自動給水装置（ブラケット式金属製網ケージでの飼育時）又は給水瓶（プラスチック製エコンケージでの飼育時）により自由に摂取させた。

飼料及び床敷中の混入物質の分析に関しては、使用したロットについて Eurofins Scientific Analytics で実施した分析結果を入手した。また、飲料水については、水道法に準拠した施設全体の水質の分析を定期的（年 4 回）に芝浦セムテック株式会社に依頼して得られたデータを入手した。これらのデータにより飼料、床敷及び飲料水中の混入物質が試験成績に影響を与える可能性のないことを確認し、分析報告書の写しを保存した。

6.6　動物の識別

動物は、番号が刻印された耳標（雄：410~471、雌：472~554）を入荷時に装着し、個体識別を行った。群分け後は、1000 の位は群（対照群、低、中及び高用量の順）、100 の位は性別（0 番を雄、1 番を雌）、10 と 1 の位は個体番号を示す 4 桁の動物番号を設定した。各飼育ケージに投与量（群）ごとに色分けしたケージラベルを付け、試験番号、投与経路、投与量、性別、動物番号、耳標番号、剖検予定日（雄及び非交配群）、交尾成立日（交配群の雌雄）及び分娩日（交配群雌）を明記した。

6.7　投与経路、投与期間及び投与回数並びに回復期間とそれらの選択理由

投与経路は毒性試験法ガイドラインに準じ、経口投与を選択した。投与期間は交配群雌雄ともに交配前 14 日、更に、雄は交配開始後 28 日（計 42 日）、交配群雌は交配期間及び妊娠期間を通して授乳 4 日まで（計 39~47 日、全児死産動物含む）、非交配群は 42 日とした。投与回数は反復投与試験で一般的に行われている 1 日 1 回とした。回復動物は 42 日の投与期間終了後、被験物質投与に起因した変化の可逆性、持続性並びに遅発性毒性等について観察するため、14 日間の回復期間を設けた。

6.8　投与方法

投与方法はげっ歯類の経口投与に際して一般的な強制経口投与とした。投与容量は 5 mL/kg 体重とし、胃ゾンデを用いて投与液を 07:55~12:29 の間に投与した。ただし、投与時に分娩中であった動物は分娩終了を待って、14:01~15:08 の間に投与した。対照群には媒体のみを同様に投与した。個体ごとの投与液量（表示単位：0.1 mL）は、直近の体重を基準に算出した。

6.9　投与量及び群構成

投与量は 40、200 及び 1000 mg/kg の 3 用量とし、試験群はこれらの用量群に媒体を投与する対照群を加え 4 群構成とした。1 群当たりの動物数は交配を行う交配群として各群で雌雄各 12 匹、交配しない非交配群として対照群及び高用量群で雌各 10 匹とした。なお、対照群及び高用量群における雄の群内番号 8 番以降の各 5 匹並びに非交配群の群内番号 18 番以降の各 5 匹は、最終投与終了日以降、回復動物とした。群構成を表 1-1.及び 1-2.に示した。

表 1-1.群構成表（雄）

試験群	投与量[注1] (mg/kg)	被験液濃度 (mg/mL)	投与容量 (mL/kg)	交配群	
				動物数	動物番号
対照群	0	0	5	12	1001~1012[注2]
低用量群	40	8	5	12	2001~2012
中用量群	200	40	5	12	3001~3012
高用量群	1000	200	5	12	4001~4012[注2]

注 1：リアクティブ　ブラック-5 の色素量として
注 2：群内番号 8 番以降の 5 匹は、最終投与終了日以降、回復動物とした。

表 1-2.群構成表（雌）

試験群	投与量[注1] (mg/kg)	被験液濃度 (mg/mL)	投与容量 (mL/kg)	交配群		非交配群	
				動物数	動物番号	動物数	動物番号
対照群	0	0	5	12	1101~1112	10	1113~1122[注3]
低用量群	40	8	5	12	2101~2112	−	−
中用量群	200	40	5	12	3101~3112	−	−
高用量群	1000	200	5	12	4101~4112	10	4113~4122[注3]

注 1：リアクティブ　ブラック-5 の色素量として
注 3：群内番号 18 番以降の 5 匹は、最終投与終了日以降、回復動物とした。

6.10　投与量の設定根拠

本試験の投与量は、先に実施した「リアクティブ　ブラック-5 のラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）、株式会社ボゾリサーチセンター、試験番号：N-R040、投与量：100、300 及び 1000 mg/kg/day」の結果（添付資料 6）[2]を参考に設定した。すなわち、被験物質の排泄による色調変化として、淡紫色尿及び/あるいは暗青色便が各被験物質投与群の雌雄にみられ、被験物質の貯留による色調変化として、腎臓の黒色化及び全身皮下を含め諸器官/組織の青色化が 1000 mg/kg 投与群の雌雄に観察された。また、被験物質の排泄経路の一つである腎臓に相対重量の高値が 300 及び 1000 mg/kg 投与群の雌に認められた。他に、1000 mg/kg 投与群の雄で総コレステロールの高値、雌で心臓の相対重量の高値が認められた。以上のことから、本試験の投与量は、投与期間が約 3 倍となること、300 及び 1000 mg/kg 投与群で腎臓の相対重量の高値が認められたことを考慮し、1000 mg/kg を高用量とし、以下公比 5 で除して、200 及び 40 mg/kg/日をそれぞれ中及び低用量に設定した。

6.11　観察及び検査の方法

試験日の起算は投与開始日を投与 1 日、投与 1 日から 7 日を投与 1 週、回復開始日（投与 42 日の翌日）を回復 1 日、回復 1 日から 7 日を回復 1 週、交尾成立日を妊娠 0 日、分娩終了日（出産日）を授乳 0 日、出生日を生後 0 日とし、以下に示す項目について、それぞれ記載の時期に観察及び検査を実施した。

全児死産母動物、交尾不成立雌動物及び妊娠 25 日未分娩動物は、体重を測定し、血液及び血液化学検査用試料として採血した後、イソフルラン麻酔下で腹大動脈切断により放血し、安楽死させ速やかに病理学検査に供した。

6.11.1　一般状態の観察

全個体について、投与期間中は毎日 3 回（投与前、投与直後及び投与 1~3 時間後）、回復期間中は毎日 2 回（午前・午後）、それぞれ生死、身体の外観、姿勢、行動及び排泄物（尿、糞）などの一般状態における異常の有無を観察した。なお、投与 2 週以降の動物のハンドリングを伴った定期的な観察は、詳細な一般状態の観察と兼ねて行った。

6.11.2　詳細な一般状態の観察、機能検査、握力及び自発運動量の測定

詳細な一般状態の観察は全個体について実施した。雄及び非交配群は投与期間中及び回復期間中毎週 1 回、交配群雌は交配前投与期間中毎週 1 回、交配期間中、妊娠期間中及び授乳期間中は指定された日（交尾動物は妊娠 1、7、14 及び 20 日、未交尾動物は交配開始後 6 及び 13 日、分娩動物は授乳 4 日）にそれぞれ行った。

機能検査、握力測定及び自発運動量の測定は、各群の 5 匹（雄の群内番号 8~12 番、交配群雌の各群の分娩順で動物番号が若い順[注 1]、非交配群の群内番号 18~22 番）について行った。投与期間中は交配群雌で授乳 4 日（投与 41~43 日）に、その他は投与 6 週（投与 38~39 日）に、回復期間中は回復 2 週（回復 10~11 日）に行った。

上記の観察、検査及び測定は、動物をランダムに配置し、観察者に対して投与量などの情報を制限（ブラインド化）した状態で行った。ただし、自発運動量の測定はブラインド化を行わなかった。なお、詳細な一般状態の観察及び機能検査の観察・検査結果について、実数データ以外はスコア化した評点法を用いて記録した。

注 1：　交配群雌の検査対象動物を以下に示した。

試験群	動物番号
対照群	1102、1104、1105、1111、1112
低用量群	2101、2102、2104、2105、2108
中用量群	3102、3104、3105、3106、3109
高用量群	4101、4104、4105、4107、4108

1)　詳細な一般状態の観察

ケージ内観察は姿勢、痙攣、異常行動を、手に持っての観察はケージからの取り出

し易さ、被毛・皮膚の状態、眼・鼻の分泌物、眼球突出、眼瞼閉鎖状態、可視粘膜、自律神経機能（流涙、流涎、立毛、瞳孔径、異常呼吸）、ハンドリングに対する反応、ハンドリング時の発声を、オープンフィールド内観察は覚醒状態、痙攣、異常行動、常同行動、歩行、姿勢、身繕い、立ち上がり回数、排泄物（排糞数、排尿）を調べた。

2) 機能検査

検査は聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射、空中正向反射、着地開脚幅とした。

3) 握力測定

機能検査に引き続き、CPU ゲージ MODEL-RX-5（アイコーエンジニアリング株式会社）を用いて前肢及び後肢の握力を測定した。

4) 自発運動量の測定

握力測定に引き続き、実験動物用自発運動センサーNS-AS01（株式会社ニューロサイエンス）を用いて自発運動量を測定した。測定時間は 1 時間とし、10 分間隔及び 0~60 分の測定値を集計した。

6.11.3 体重測定

全個体について、雄及び非交配群は投与 1、8、15、22、29、36、42 日及び剖検日に、回復動物は更に回復 1、8、14 日及び剖検日に、交配群雌は投与 1、8 及び 15 日（ただし、未交尾動物は 22 日）、妊娠 0、7、14 及び 20 日、授乳 0 及び 4 日並びに剖検日に体重を測定した。なお、午後の分娩観察時における授乳 0 日の体重測定は 13:35~16:30 の間に実施し、その他の体重測定は測定日の 08:28~11:36 の間（投与期間中は投与前）に行った。剖検日は前日から約 16 時間絶食させた後、相対器官重量算出に備えて体重を 07:43~09:09 の間に、全児死産母動物、交尾不成立雌動物及び妊娠 25 日未分娩動物は飼育室から搬出する前に、それぞれ体重測定したが、いずれも統計解析から除外した。

6.11.4 摂餌量測定

雄及び非交配群は投与 2、8、15、30、36 及び 42 日に、回復動物は更に回復 1、8 及び 14 日に、交配群雌は投与 2、8 及び 15 日、妊娠 1、7、14 及び 20 日並びに授乳 2 及び 4 日に残餌量を測定し、前日の給餌量との差から 1 匹当たりの 1 日摂餌量を算出した。給餌量及び残餌量の測定は測定日の 08:28~11:41 の間（投与期間中は投与前）に行った。なお、1000 mg/kg 投与群の雄 1 例（動物番号 4010）は投与 8 日以降 18 日まで切歯破損がみられ摂食不足が予想されたため、投与 8 日の摂餌量測定後から投与 19 日までは粉砕飼料を給餌した。したがって、本動物の投与 15 日の摂餌量測定値（32 g）は粉砕飼料での測定となったが、同群の雄と摂食量に差はみられず、統計解析は本動物の測定値も含めて実施した。

6.11.5　膣垢検査

交配群雌の全個体について、投与開始日から交尾成立まで毎日（午前）、膣垢を採取した。交配前投与期間中の標本は、多数の角化上皮細胞から成る膣垢像を発情の指標とし、発情回数及び発情期から次の発情期までの日数（性周期）、観察雌個体数に対する性周期異常を示した個体数の割合を調べた。交配期間中の標本は膣垢内の精子の有無を調べるのに加え、膣垢像を発情前期(P)、発情期(E)、発情後期(M)及び発情休止期(D)に分類した。

非交配群は、投与期間終了時及び回復期間終了時の剖検 6 日前から剖検日まで毎日（午前）膣垢を採取し、鏡検した。鏡検結果は、剖検時における性周期ステージの判別のための参考データとした。なお、P→E→M→D（→P）の順序で周期的変化を示し、4 又は 5 日の周期を繰り返す個体を正常、それ以外を性周期異常とした。

6.11.6　交配方法

交配前投与期間終了後、交配群の同じ投与群の雌雄を 1:1 で終夜同居させ、翌朝、膣栓形成あるいは膣垢中に精子を確認したものを交尾成立とみなした。交配開始日を 0 日と起算して交尾までに要した日数を求めた。同一雌雄による同居期間は最長 14 日間であった。交尾が成立しない雌（動物番号 2112）は、交配期間終了日を妊娠 0 日と仮定して一般状態の観察、体重・摂餌量測定及び投与を継続し、25 日後に諸検査を行ったが、この動物の妊娠期間中のデータは統計解析から除外した。

6.11.7　分娩及び哺育観察

1)　母動物の観察

交尾の確認された雌動物は、妊娠 21 日から妊娠 25 日の午前まで 1 日 2 回（午前・午後、妊娠 25 日は午前に 1 回）、分娩の有無並びにその終了を確認するとともに分娩状態の異常の有無（胎盤及び羊膜の処理の有無など）を観察した。交尾成立から分娩終了までを妊娠期間とし、妊娠期間を 0.5 日単位で求めた。ただし、1 日単位で集計した。なお、分娩終了の確認は 17:00 までとした。

分娩が終了した母動物は授乳 4 日まで出生児を哺育させ、哺育状態（児集め、営巣及び授乳など）を観察し、授乳 5 日に病理学検査に供した。なお、妊娠 25 日の午前までに分娩が終了しなかった 40 mg/kg 投与群の 2 例（動物番号 2109 及び 2110）及び 200 mg/kg 投与群の 1 例（動物番号 3110）は、イソフルラン麻酔下で採血後、腹大動脈切断により放血致死させ、病理学検査に供した。それらの動物の妊娠の有無を確認した結果、着床が認められなかったため不妊とみなした。また、分娩 0 日に全児死産であった母動物（動物動物 1107）は、その時点で同様に検査を行った。

2)　出生児の観察

生後 0 日に出生児数及び死産児数を数え、合わせて出産児数とした。出産児の外表異常[注)]の有無を観察して性別を確認した。出生児は体重を個体別に測定した後、母動物に哺育させた。死産児はブアン液で固定して保存した。

出生児は生後 4 日まで毎日 1 回、死亡児の有無を確認した。死亡児は肉眼による異常の有無を観察した後、ブアン液で固定して保存した。生後 4 日に全生存児の性別を判定し、個体別に体重を測定後、肉眼による異常の有無を観察した後、イソフルラン深麻酔下でブアン液に浸漬し、固定して保存した。

注）：頭部の陥没や裂、顔面の鼻吻や上下顎、口唇のゆがみや裂、眼瞼や耳介の大きさ、形状、左右のバランス、胸胴部のゆがみや大きさ、内部臓器の突出、尾部の長さ、形状、数、欠損、四肢部の長さ、形状、指の数、欠損及び左右のバランスに注意して観察し、正常と異なる場合を異常とした。

6.11.8　尿検査（摂水量測定を含む）

検査は、投与期間終了週（投与 6 週、投与 37~38 日）及び回復期間終了週（回復 2 週、回復 9~10 日）に行った。投与期間中は検査当日の投与後に各群の 5 匹（雄の群内番号 8~12 番、非交配群の群内番号 18~22 番）について、回復期間中は回復動物の全個体について、それぞれ採尿器をセットしたケージに収容し、絶食・自由摂水下で 4 時間尿を、次いで自由摂食・自由摂水下でその後の 20 時間尿を採取した。検査項目を表 2.に示した。採取した最初の 4 時間尿について pH 以下沈渣までの検査と尿量を、その後に得られた 20 時間尿について浸透圧、電解質（ナトリウム、カリウム、塩素）及び尿量の測定を行った。尿量は 4 時間の尿量と 20 時間の尿量を合計して 1 日量を算出した。電解質は 20 時間尿について濃度を測定し、測定濃度と 24 時間の尿量から 1 日当たりの排泄量を算出した。摂水量は採尿器をセットしたケージに収容した状態で前日からの 1 日の摂取量を、給水瓶を用いて測定した。

表 2.尿検査の項目、測定法及び使用機器など

検査項目	測定方法
pH	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
たん白質	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
ケトン体	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
グルコース	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
潜血	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
ビリルビン注)	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
総ビリルビン(T-BIL)注)	ビリルビンオキシダーゼ法 c)
ウロビリノーゲン	ﾏﾙﾃｨｽﾃｨｯｸｽ試験紙［ｼｰﾒﾝｽﾍﾙｽｹｱ・ﾀﾞｲｱｸﾞﾉｽﾃｨｸｽ株式会社］a)
色調	肉眼観察
沈渣	鏡検法
尿量（4 時間量）	目盛付スピッツ管を用いた容量測定（単位：mL）
浸透圧	氷点降下法 b)（単位：mOsm/kg）
ナトリウム	イオン選択電極法 c)（単位：mmol/24h）
カリウム	イオン選択電極法 c)（単位：mmol/24h）
塩素	イオン選択電極法 c)（単位：mmol/24h）
尿量（20 時間量）	メスシリンダーを用いた容量測定（単位：mL）
摂水量（24 時間量）	重量測定

使用測定機器
a)：尿自動分析装置　クリニテック 500（Siemens Healthcare Diagnostics Inc.）
b)：自動浸透圧測定装置 オートアンドスタット OM-6030（アークレイ株式会社）
c)：臨床化学自動分析装置　TBA-120FR 形（東芝メディカルシステムズ株式会社）

注）：試験紙法によるビリルビン検査結果から薬物干渉による偽陽性が示唆されたため、追加測定として、ビリルビンオキシダーゼ法による総ビリルビンを測定した。ビリルビンオキシダーゼ法による測定は、試験紙法で使用した同一サンプルを用いて、投与 6 週及び回復 2 週ともに実施した。

6.11.9　血液学検査

計画剖検対象動物について、剖検前日（最終投与日あるいは回復 14 日）から一夜（約 16~21 時間）絶食させた。各群雌雄各 5 匹（動物番号が若い順、ただし、交配群雌は分娩順の 5 匹）、交尾不成立雌動物、妊娠 25 日未分娩動物及び全児死産した母動物について、イソフルラン麻酔下に開腹し、腹大動脈から EDTA-2K 加採血瓶（SB-41：シスメックス株式会社）に血液を採取した。得られた血液について、次の表 3.-1)に記載した項目及び方法により検査した[注 1]。なお、採血した全例について、May-Grünwald-Giemsa 染色法による血液塗抹標本を作製した。また、3.8%クエン酸ナトリウム溶液加試験管（血液 9 容に対し 1 容の割合）に採取した血液を遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血漿について表 3.-2)に記載の項目及び方法により検査した。なお、採血で得られた血漿が被験物質あるいはその代謝物由来による青色を呈した。しかし、測定系に影響を及ぼさないことを確認した上で、そのまま測定値を採用した。

注 1：　交配群雌の検査対象動物を以下に示した。

試験群	動物番号			
	母動物	妊娠 25 日 未分娩動物	交尾不成立動物	全児死産母動物
対照群	1102、1104、1105、1111、1112	なし	なし	1107
低用量群	2101、2102、2104、2105、2108	2109、2110	2112	なし
中用量群	3102、3104、3105、3106、3109	3110	なし	なし
高用量群	4101、4104、4105、4107、4108	なし	なし	なし

表 3.血液学検査の項目、測定法及び使用機器など

1）EDTA-2K 加血液についての検査		
検査項目	測定方法	単位
赤血球数(RBC)	2 角度レーザーフローサイトメトリー法 a)	$10^4/\mu L$
ヘモグロビン量(HGB)	シアンメトヘモグロビン変法 a)	g/dL
ヘマトクリット値(HCT)	赤血球数及び平均赤血球容積から算出 a)	%
平均赤血球容積(MCV)	2 角度レーザーフローサイトメトリー法 a)	fL
平均赤血球血色素量(MCH)	赤血球数及びヘモグロビン量から算出 a)	pg
平均赤血球血色素濃度(MCHC)	ヘモグロビン量及びヘマトクリット値から算出 a)	g/dL
網赤血球率(Retic)	RNA 染色によるレーザーフローサイトメトリー法 a)	%
血小板数(PLT)	2 角度レーザーフローサイトメトリー法 a)	$10^4/\mu L$
白血球数(WBC)	2 角度レーザーフローサイトメトリー法 a)	$10^2/\mu L$
白血球百分率注)	ペルオキシダーゼ染色によるフローサイトメトリー法 +2 角度レーザーフローサイトメトリー法 a)	%
白血球各細胞の絶対数注)	ペルオキシダーゼ染色によるフローサイトメトリー法 +2 角度レーザーフローサイトメトリー法 a)	$10^2/\mu L$
2）クエン酸ナトリウム加血液から分離した血漿についての検査		
検査項目	測定方法	単位
プロトロンビン時間(PT)	クロット法 b)	s
活性化部分トロンボプラスチン時間(APTT)	クロット法 b)	s
フィブリノーゲン量(FIB)	トロンボプラスチン法 b)	mg/dL
使用測定機器 a)：総合血液学検査装置　アドヴィア 120（Siemens Healthcare Diagnostics Inc., Illinois, USA） b)：血液凝固自動分析装置　ACL Elite Pro（Instrumentation Laboratory, MA, USA）		
注）：好中球(Neut.)、好酸球(Eosino.)、好塩基球(Baso.)、リンパ球(Lymph.)、単球(Mono.)及び大型非染色球(LUC)		

6.11.10　血液化学検査

血液学検査用試料と同時に採取した血液を凝固促進剤入り試験管（ベノジェクト II-オートセップ：テルモ株式会社）に採り、遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血清について表 4.-1)に記載の項目及び方法により検査した。また、ヘパリン加試験管（血液 1 mL 当たり約 20 単位のヘパリン）に採取した血液を遠心分離（設定：3,100 rpm、1,690×g、12 分間）し、得られた血漿について表 4.-2)に記載の項目及び方法により検査した。血清の一部（交尾不成立雌動物、妊娠 25 日未分娩動物及び全児死産母動物を除く）は血中ホルモン測定用に約 0.5 mL×3 本をサンプルチューブに分注し、残余の血清と共に−80°C の冷凍庫（許容範囲：−70°C 以下）に保存した。なお、採血で得られた血漿及び血清が、被験物質あるいはその代謝物由来による青色を呈した。しかし、測定系に影響を及ぼさないことを確認した上で、測定値をそのまま採用した。

表 4.血液化学検査の項目、測定法及び使用機器など

1）分離した血清についての検査		
検査項目	測定方法	単位
ALP	Bessey-Lowry 法 [a)]	IU/L
総胆汁酸（TBA）	3α-ヒドロキシステロイドデヒドロゲナーゼ [a)]	μmol/L
総コレステロール(T-CHO)	CEH-COD-POD 法 [a)]	mg/dL
トリグリセライド(TG)	LPL-GK-GPO-POD 法 [a)]	mg/dL
リン脂質(PL)	PLD-ChOD-POD 法 [a)]	mg/dL
総ビリルビン(T-BIL)	ビリルビンオキシダーゼ法 [a)]	mg/dL
グルコース(GLU)	グルコースデヒドロゲナーゼ法 [a)]	mg/dL
尿素窒素(BUN)	Urease-LEDH 法 [a)]	mg/dL
クレアチニン(CRNN)	Creatininase-creatinase-sarcosine oxidase-POD 法 [a)]	mg/dL
ナトリウム(Na)	イオン選択電極法 [a)]	mmol/L
カリウム(K)	イオン選択電極法 [a)]	mmol/L
塩素(Cl)	イオン選択電極法 [a)]	mmol/L
カルシウム(Ca)	OCPC 法 [a)]	mg/dL
無機リン(P)	モリブデン酸法 [a)]	mg/dL
総たん白質(TP)	Biuret 法 [a)]	g/dL
アルブミン(ALB)	BCG 法 [a)]	g/dL
A/G 比	総たん白質及びアルブミンから算出	
2）ヘパリン加血液から分離した血漿についての検査		
検査項目	測定方法	単位
AST	UV-rate 法 [a)]	IU/L
ALT	UV-rate 法 [a)]	IU/L
LDH	UV-rate 法 [a)]	IU/L
γ-GTP	L-γ-グルタミル-3-カルボキシ-4-ニトロアニリド法 [a)]	IU/L
使用測定機器 a)：臨床化学自動分析装置　TBA-120FR 形（東芝メディカルシステムズ株式会社）		

6.11.11　血中ホルモン測定

他の観察及び検査結果から下垂体-甲状腺系への影響が認められなかったため 6.11.10 で得られた血清について血中ホルモン（T_3、T_4及び TSH）測定は実施しなか

った。

6.11.12　病理学検査

1)　剖検及び器官重量測定

最終投与翌日及び回復期間終了日に、イソフルラン麻酔下で採血した動物は採血後に、その他の動物はイソフルラン麻酔下で腹大動脈切断により放血致死させ、それぞれ体外表並びに頭部、胸部及び腹部の器官・組織の肉眼検査を行った。不妊であった妊娠 25 日未分娩動物及び交尾不成立雌動物並びに全児死産母動物は、採血して放血致死させた後、速やかに病理学検査に供した。なお、交配群の雌動物については剖検時に黄体数及び着床痕数を数えた。次いで、全個体について、以下に示す器官の重量を測定した。それら器官重量（絶対重量）と剖検時の体重から体重 100 g 当たりの相対重量を算出し、*印をつけた両側性の器官は左右別々に測定し、その合計値で評価した。なお、不妊であった妊娠 25 日未分娩動物、交尾不成立雌動物及び全児死産母動物についても同様に器官重量を測定したが、剖検日の体重も含め統計解析の対象から除外した。

脳、下垂体、甲状腺*（上皮小体を含む）、副腎*、胸腺、脾臓、心臓、肝臓、腎臓*、精巣*、精巣上体*、前立腺、精嚢（凝固腺を含む）、卵巣*、子宮

2)　病理組織学検査

全ての個体について、以下に示す全検査対象器官/組織をリン酸緩衝 10 vol%ホルマリン液で固定し、保存した。肺は、固定時にリン酸緩衝 10 vol%ホルマリン液を注入した。ただし、眼球、視神経はリン酸緩衝液で調製した 3 vol%グルタルアルデヒド・2.5 vol%ホルマリン液で固定後、精巣及び精巣上体はブアン液で固定した後、リン酸緩衝 10 vol%ホルマリン液に置換し保存した。次いで、パラフィン包埋した後、切片とし（下線を施した器官・組織は固定・保存のみとした）、ヘマトキシリン・エオジン（H・E）染色標本を作製した。

鏡検は、まず投与終了時剖検群における対照群及び高用量群の採血を行った動物、不妊であった妊娠 25 日未分娩動物及びその交配相手雄、交尾不成立雌動物及びその交配相手雄並びに全児死産母動物の全検査対象器官/組織ついて行った。両側性の器官については両側を摘出し、坐骨神経、眼球、甲状腺、上皮小体、副腎、顎下腺、腎臓、大腿骨（骨髄を含む）及び大腿部骨格筋は片側、精巣、卵巣、精巣上体及び精嚢（凝固腺含む）は両側並びに子宮は両角部を鏡検した。なお、舌下腺及び視神経は H･E 染色標本作製までとし、病理組織学検査は実施しなかった。また、肉眼的異常部位は対照群及び高用量群の検査対象動物、回復動物の全例について検査した。その結果、雌雄の胃、盲腸、結腸、直腸及び膀胱並びに雄の腎臓については、被験物質投与の影響が疑われたため、低、中用量群及び回復動物についても検索を行った。

大脳、小脳（橋を含む）、坐骨神経、脊髄（胸部）、眼球、視神経、ハーダー腺、下垂体、甲状腺、上皮小体、副腎、胸腺、脾臓、顎下リンパ節、腸間膜リンパ節、心臓、胸大動脈、気管、肺（気管支を含む）、舌、喉頭、食道、胃、十二指腸、空腸、回腸（パイエル板を含む）、盲腸、結腸、直腸、顎下腺、舌下腺、肝臓、膵臓、腎臓、膀胱、精巣、卵巣、精巣上体、子宮、腟、前立腺、精嚢（凝固腺を含む）、皮膚（鼠径部）、乳腺（鼠径部）、胸骨（骨髄を含む）、大腿骨（骨髄を含む）、大腿部骨格筋、個体識別部（耳標を装着した耳介）及び肉眼的異常部位

更に、雄の 200 mg/kg 及び 1000 mg/kg 群で尿細管上皮細胞の好酸性小体が観察されたため、代表例（動物番号 1001、3001、4001）の腎臓について、抗 α2u グロブリン抗体を用いた免疫組織化学染色標本及び PAS 染色標本を作製し、鏡検した。

6.12　統計解析

6.12.1　　パラメータの算出

以下の式により、性周期異常率、交尾率、授精率、受胎率及び出産率は群ごとに、妊娠期間、着床率、分娩率、死産児率、外表異常率、出生率、生後 4 日生存率、生後 0 及び 4 日の性比は母動物（腹）ごとに算出した。なお、出生児の体重は母動物ごと雌雄別に平均値を求めた。

性周期異常率(%) =（性周期異常を示した個体数/観察雌個体数）×100
交尾率(%) =（交尾動物数/同居動物数）×100
授精率(%) =（雌を妊娠させた雄の数/交尾した雄の数）×100
受胎率(%) =（妊娠した雌の数/交尾した雌の数）×100
出産率(%) =（出生児出産雌数/妊娠雌数）×100
妊娠期間(日) = 妊娠 0 日から分娩した日までの日数
着床率(%) =（着床痕数/黄体数）×100
分娩率(%) =（出産児数/着床痕数）×100
死産児率(%) =（死産児数/出産児数）×100
外表異常率(%) =（外表異常児数/出産児数）×100
出生率(%) =（出生児数/出産児数）×100
生後 4 日生存率(%) =（生後 4 日の生存児数/出生児数）×100
生後 0 日（死産児含む）の性比 = 雄出産児数/出産児数
生後 0 日（出生児）の性比 = 雄出生児数/出生児数
生後 4 日の性比 = 生後 4 日の雄生存児数/生後 4 日の生存児数

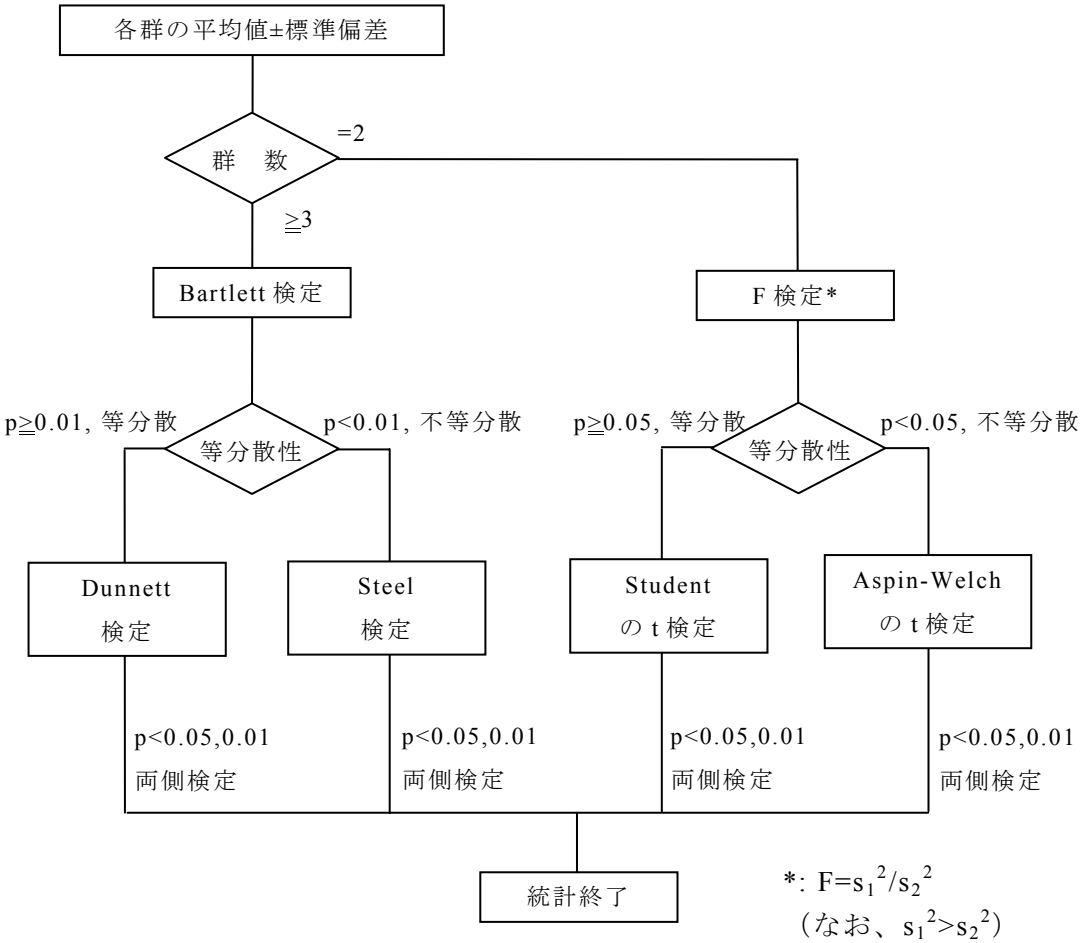
6.12.2　　検定

対照群と各用量群との差については、以下の手法により統計学的有意性の検定を行

った。

体重、体重増加量（雄及び非交配群：投与 1~42 日及び回復 1~14 日、交配群雌：投与 1~15 日、妊娠 0~20 日及び授乳 0~4 日、出生児：生後 0~4 日）、摂餌量、摂水量、発情期像発現回数、性周期（発情周期）、交尾までに要した日数、妊娠期間、黄体数、着床痕数、生存児数、性比（生後 0 及び 4 日）、オープンフィールド内観察（排糞数、立ち上がり回数）、機能検査（着地開脚幅）、握力及び自発運動量、尿検査の定量的項目[注)]、血液学検査、血液化学検査及び器官重量（含、剖検時体重）は、群ごとに平均値及び標準偏差を求め、次に示す模式図の方法に従って検定した[3][4][5]。

注）：4 時間尿のビリルビンオキシゲナーゼ法による総ビリルビン測定は除く。



着床率、分娩率、出生率、死産児率、外表異常率及び生後 4 日生存率は、群ごとに平均値及び標準偏差を求め、Steel 検定（有意水準 0.05 及び 0.01、両側）を行った[5]。

性周期異常率、交尾率、授精率、受胎率及び出産率並びに聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射の各反応・反射率は、各群の性周期異常を示した個体数、交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、出生児出

産雌動物数、正常反射のみられた動物数より算出し、期待度数が 5 以下のセルがみられたため、Fisher の直接確率計算法により検定（有意水準 0.05 及び 0.01、両側）を行った[6]。

7. 試験結果

7.1 一般状態（Table 1-1~1-11、Appendix 1-1~1-34）

1) 投与期間

いずれの投与群においても死亡動物はみられなかった。

着色糞（濃青色）、着色尿（淡紫色）及び全身皮膚の青色化がみられた。発現状況は以下の通りであった。

性	投与量 (mg/kg)	発現状況		
		着色糞（濃青色）	着色尿（淡紫色）	全身皮膚の青色化
雄	40	投与3日以降9例で一過性又は散発的	なし	なし
	200	投与2日以降全例でほぼ継続	なし	なし
	1000	投与2日以降全例でほぼ継続	投与1日以降11例で一過性、散発的又は断続的	なし
交配群雌	40	投与3~12日に6例で一過性、散発的又は断続的	なし	なし
	200	投与2日以降全例でほぼ継続	なし	なし
	1000	投与2日以降全例でほぼ継続	投与1日~妊娠6日に9例で一過性又は散発的	なし
非交配群	1000	投与2日以降全例でほぼ継続	投与1日以降8例で一過性又は散発的	投与33日以降3例で継続

なお、哺育期間中の母動物の着色糞及び着色尿の症状観察については、母動物へのストレスを避けるために着色糞及び着色尿による着色した床敷は除去しなかった。したがって､症状が観察された日以降は､床敷交換日まで断続的に症状を記録し続けた。また、交配期間中の着色糞、着色尿については、雌雄いずれの排泄物か確認できないため、評価から除外した。

その他、1000mg/kg投与群で以下の所見がみられた。

性	投与量(mg/kg)	動物番号	症状	発現期間
雄	1000	4010	切歯破損	投与8~18日
非交配群	1000	4121	尿道口周囲の腫脹	投与8日以降剖検時

なお、対照群の1例（動物番号1107）で分娩日に腟脱がみられたが、全児死産動物であった。

2) 回復期間

着色糞、着色尿及び全身皮膚の青色化が 1000 mg/kg 投与群でみられた。しかし、雄の着色糞は回復3日に、着色尿は回復2日に、雌の着色糞及び着色尿ともに回復2日に、全身皮膚の青色化は回復6日にそれぞれ消失した。

投与期間中にみられた尿道口周囲の腫脹の1例（動物番号4121）は、回復期間中も継続してみられた。

7.2　詳細な一般状態の観察、機能検査、握力測定及び自発運動量の測定（Fig. 1~5、Table 2-1~2-84、Appendix 2-1~2-258）

7.2.1　ホームケージ内観察（Table 2-1~2-23、Appendix 2-1~2-72）

いずれの動物にも異常はなかった。

7.2.2　手に持っての観察（Table 2-24~2-46、Appendix 2-73~2-144）

1)　投与期間

非交配群の 1000 mg/kg 投与群で皮膚の青色化が投与 6 週に 3 例（動物番号 4119、4120 及び 4121、いずれも回復動物）みられた。

2)　回復期間

投与 6 週に皮膚の青色化がみられた 3 例は、回復 1 週時にも引き続きみられたが、投与 2 週時点で消失した。

7.2.3　オープンフィールド内観察（Table 2-47~2-69、Appendix 2-145~2-216）

雄、交配群雌及び非交配群のいずれの動物においても、検査項目に異常はなく、立ち上がり回数及び排糞数にも対照群と各被験物質投与群の間に有意差は認められなかった。

7.2.4　機能検査（Table 2-70~2-74、Appendix 2-217~2-230）

1)　投与期間終了週検査

雄、交配群雌及び非交配群のいずれの動物においても、聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はなかった。

着地開脚幅では、雄、交配群雌及び非交配群の各被験物質投与群ともに、対照群との間に有意差は認められなかった。

2)　回復期間終了週検査

いずれの動物にも聴覚反応、接近反応、接触反応、痛覚反応、瞳孔反射及び空中正向反射に異常はなかった。

着地開脚幅では、1000 mg/kg 投与群の雌雄ともに対照群との間に有意差は認められなかった。

7.2.5　握力（Table 2-75~2-79、Appendix 2-231~2-244）

1)　投与期間終了週検査

雄、交配群雌及び非交配群の各被験物質投与群ともに、対照群との間に有意差は認められなかった。

2)　回復期間終了週検査

1000 mg/kg 投与群の雌雄ともに、対照群との間に有意差は認められなかった。

7.2.6　自発運動量（Fig. 1~5、Table 2-80~2-84、Appendix 2-245~2-258）

1)　投与期間終了週検査

雄、交配群雌及び非交配群の各被験物質投与群ともに、対照群との間に有意差は認められなかった。

2)　回復期間終了週検査

1000 mg/kg 投与群の雌雄ともに、対照群との間に有意差は認められなかった。

7.3　体重（Fig. 6~8、Table 3-1~3-7、Appendix 3-1~3-22）

1)　投与期間

雄及び非交配群では､対照群と各被験物質投与群の間に有意差は認められなかった。

交配群雌では、各被験物質投与群ともに交配前、妊娠及び授乳期間を含め各測定値に有意差は認められなかったが、妊娠期間中の体重増加量が 200 及び 1000 mg/kg 投与群で有意な高値を示した。これは対照群に比べ胎児が多かったためであり、偶発的変化と判断した。

2)　回復期間

雄では、対照群と 1000 mg/kg 投与群の間に有意差は認められなかった。

雌では、1000 mg/kg 投与群で体重増加量の有意な低値が認められたが、各測定値の間に有意差がなく、摂餌量にも被験物質投与の影響がないこと、投与期間中からの体重推移をみると、投与期間終了時の剖検により回復 1 日の対照群の平均体重がわずかに低値であったことによる偶発的変化と判断した。

7.4　摂餌量（Fig. 9~11、Table 4-1~4-7、Appendix 4-1~4-22）

1)　投与期間

雄及び非交配群では、対照群と各被験物質投与群との間に有意差は認められなかった。

交配群雌では、1000 mg/kg 投与群で授乳 4 日に有意な高値が認められたが、対照群より生後 4 日の出生児数が多かったことによる母動物の摂餌量摂取であり、被験物質投与との関連はないと判断した。

2)　回復期間

1000 mg/kg 投与群の雌雄ともに、対照群との間に有意差は認められなかった。

7.5　尿検査（摂水量測定を含む）（Table 5-1~5-16、Appendix 5-1~5-30）

投与 6 週の雄及び非交配群の 1000 mg/kg 投与群の全例で淡紫色の尿がみられ、投与 6 週及び回復 2 週検査でビリルビン陽性例が多くの動物にみられた。ビリルビンオキシダーゼ法によって定量的に検査した結果、全て 0.0 mg/dL であり、着色尿による試験紙への干渉によるものと考えられ、毒性学的意義はない。

1)　投与期間終了週検査

雄では、1000 mg/kg 投与群でナトリウムの尿中排泄量に有意な高値が認められた。

その他、尿検査当日の投与時に爪を剥がし、出血したことによる潜血陽性（+++）が 200 mg/kg 投与群で 1 例（動物番号 3012）みられた。

非交配群では、1000 mg/kg 投与群でナトリウムの尿中排泄量に有意な高値が認められた。

その他、尿道口周囲の腫脹がみられた 1000 mg/kg 投与群の 1 例（動物番号 4121）で潜血陽性（++）がみられ、沈渣で赤血球及び白血球陽性（++）であった。

2)　回復期間終了週検査

雄では、1000 mg/kg 投与群 1 例（動物番号 4011）で褐色尿がみられたが、1 例のみであり、投与期間終了時検査にはみられず、他の検査項目に異常がないことから、偶発的変化と判断した。

その他、対照群の雄 1 例（動物番号 1008）で潜血陽性（+++）がみられたが、被験物質投与との関連はない。

7.6　血液学検査（Table 6-1~6-10、Appendix 6-1~6-28）

1)　投与期間終了時検査

雄では、1000 mg/kg 投与群でプロトロンビン時間の有意な延長が認められた。

交配群雌では、対照群と各被験物質投与群との間に有意差は認められなかった。

非交配群では、1000 mg/kg 投与群でフィブリノーゲン量の有意な低値が認められた。

2)　回復期間終了時検査

雌雄ともに、対照群と 1000 mg/kg 投与群の間に有意差は認められなかった。

7.7　血液化学検査（Table 7-1~7-10、Appendix 7-1~7-28）

1)　投与期間終了時検査

雄では、1000 mg/kg 投与群で総胆汁酸の高値及びカリウム及び塩素の有意な低値が認められた。

交配群雌では、1000 mg/kg 投与群で尿素窒素の有意な高値が認められた。

非交配群では、1000 mg/kg 投与群で塩素の有意な低値が認められた。

その他、非交配群の 1000 mg/kg 投与群で総ビリルビンの有意な低値が認められたが、高値ではなく低値であり、毒性学的意義はない。

2)　回復期間終了時検査

雄では、1000 mg/kg 投与群で総胆汁酸の有意な高値が認められた。

雌では、1000 mg/kg 投与群でナトリウム及び塩素の有意な低値が認められたが、軽度な変化であった。

7.8　器官重量（Table 8-1~8-10、Appendix 8-1~8-48）

1)　投与期間終了時検査

雄では、200 及び 1000 mg/kg 投与群で腎臓の相対重量の有意な高値が認められた。

交配群雌では、1000 mg/kg 投与群で腎臓の絶対重量の有意な高値が認められた。

非交配群では、1000 mg/kg 投与群で腎臓の絶対重量に有意な高値、肝臓の相対重量に有意な高値が認められた。

2)　回復期間終了時検査

雄の 1000 mg/kg 投与群で心臓の相対重量の有意な低値が認められた。

7.9　剖検所見（Table 9-1~9-7、Appendix 9-1~9-116）

被験物質投与による器質的障害はみられなかった。

1)　投与期間終了時検査

以下に所見を示す。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	40	200	1000	0	40	200	1000	0	1000
動物数	7	12	12	7	11	9	11	12	5	5
全身皮下の青色化	0	0	0	4	0	0	0	3	0	5
腎臓の黒色化（両側）	0	0	0	5	0	0	0	5	0	5
肺の黒色巣	0	0	0	1	0	0	0	0	0	0
境界縁の肥厚	0	0	0	1	0	0	0	1	0	0
腺胃部の暗赤色巣	1	0	0	0	1	1	0	2	0	0
精巣の青色化（両側）	0	0	0	4						

上記変化のうち、全身皮下の青色化、腎臓の黒色化及び精巣の青色化は組織学的に異常なかった。また、1000 mg/kg 投与群の雄でみられた肺の黒色巣は組織学的に黒色色素を貪食したマクロファージの細胞浸潤であり、投与液のごく少量が肺に吸引されたものと考えられた。腺胃部の暗赤色巣は組織学的に軽微なびらん（雄と 1000 mg/kg 投与群の交配群雌、他の動物の組織学検査は未実施）であった。

未交尾及び交尾は認められたが相手雌が不妊（未分娩）であった動物に肉眼的異常はなかった。

性	未交尾		交尾は認められたが相手雌が不妊（未分娩）	
	雄	雌	雄	雌
40 mg/kg	2012	2112	2009、2010	2109、2110
200 mg/kg			3010	3110

全児死産が対照群の 1 例（動物番号：1107）にみられた。この母動物は妊娠 23 日から分娩が始まり、妊娠 24 日に死産児 1 例を娩出した。剖検で胎児がみられた左子宮角部の脱出、子宮の壁肥厚（組織学的には筋層の水腫及び子宮内膜増殖を伴った軽度な炎症）、黄体数 4 ヶ、着床痕数 1 ヶであった。全児死産の原因は胎児が 1 例と少なく、かつ大きくなりすぎたため娩出できなかったためと考えられた。このように胎児が 1 例で大きくなりすぎた場合、しばしばみられる変化であり、対照群の変化であ

ることから、被験物質投与との関連はない。

2) 回復期間終了時検査

以下に所見を示す。

性	雄		非交配群	
投与量（mg/kg）	0	1000	0	1000
動物数	5	5	5	5
精巣の青色化（両側）	0	3		
腎臓の黒色化（両側）	0	0	0	1
肝臓の黒色化	0	0	0	1
腺胃部の暗赤色巣	0	0	1	0

また、非交配群の 1 例（動物番号 4121）において、膀胱の壁肥厚、膀胱結石及び尿道口周囲の腫脹がみられた。

なお、精巣の青色化及び腎臓の黒色化は組織学的に異常なかった。肝臓の黒色化は組織学的に赤血球貪食によるクッパー細胞の色素沈着、腺胃部の暗赤色巣は腺胃の軽微なびらんであった。いずれも発現状況から偶発的変化と判断した。

7.10 病理組織学検査（Table 10-1~10-17、Appendix 9-1~9-116）

1) 投与期間終了時検査

被験物質投与による影響が腺胃、大腸（盲腸、結腸、直腸）、腎臓及び下部尿路組織（膀胱）にみられた。以下に詳細を記す。

【胃】

腺胃粘膜の過形成（軽微又は軽度）及び境界縁の扁平上皮細胞過形成（軽微又は軽度）が、雄、交配群雌及び非交配群の 1000 mg/kg 投与群にみられた。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	40	200	1000	0	40	200	1000	0	1000
動物数	5	8	6	5	6	8	6	5	5	5
腺胃粘膜上皮の過形成	0	0	0	5	0	0	0	3	0	4
軽微	0	0	0	2	0	0	0	2	0	2
軽度	0	0	0	3	0	0	0	1	0	2
境界縁の扁平上皮過形成	0	0	0	5	0	0	0	4	0	5
軽微	0	0	0	1	0	0	0	2	0	0
軽度	0	0	0	4	0	0	0	2	0	5

【大腸（盲腸、結腸及び直腸）】

粘膜のびまん性過形成（軽微）が、直腸では雄、交配群雌及び非交配群の 1000 mg/kg 投与群に、盲腸では雄及び非交配群の 1000 mg/kg 投与群に、結腸では雄の 1000 mg/kg 投与群にみられた。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	40	200	1000	0	40	200	1000	0	1000
動物数	5	8	6	5	6	8	6	5	5	5
盲腸										
粘膜のびまん性過形成	0	0	0	4	0	0	0	0	0	4
軽微	0	0	0	4	0	0	0	0	0	4
結腸										
粘膜のびまん性過形成	0	0	0	3	0	0	0	0	0	0
軽微	0	0	0	3	0	0	0	0	0	0
直腸										
粘膜のびまん性過形成	0	0	0	3	0	0	0	1	0	2
軽微	0	0	0	3	0	0	0	1	0	2

【腎臓】

尿細管の好酸性小体の増加が、雄の 200 及び 1000 mg/kg 投与群でみられた。尿細管上皮細胞の好酸性小体は抗 α2u グロブリン抗体による免疫組織化学染色標本で陽性を示し、PAS 染色で陰性を示したことから、α2u グロブリンに由来した物質と考える。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	40	200	1000	0	40	200	1000	0	1000
動物数	5	8	6	5	5	0	0	5	5	5
尿細管の好酸性小体の増加	0	0	3	4	0			0	0	0
軽微	0	0	3	0	0			0	0	0
軽度	0	0	0	4	0			0	0	0

【下部尿路系組織（膀胱）】

膀胱の移行上皮のびまん性過形成が、雄、交配群雌及び非交配群の 1000 mg/kg 投与群でみられた。

性	雄				交配群雌				非交配群	
投与量（mg/kg）	0	40	200	1000	0	40	200	1000	0	1000
動物数	5	8	6	5	5	5	5	5	5	5
移行上皮のびまん性過形成	0	0	0	1	0	0	0	1	0	3
軽微	0	0	0	0	0	0	0	0	0	2
軽度	0	0	0	1	0	0	0	1	0	1

2) 回復期間終了時検査

被験物質投与による影響が胃、腎臓及び下部尿路系組織にみられた。なお、投与期間中にみられた大腸の変化は、回復期間終了時には消失した。

【胃】

投与期間と同様に、境界縁の扁平上皮細胞過形成（軽微又は軽度）が雄及び非交配

群の 1000 mg/kg 投与群にみられたが、その程度及び頻度は軽減し、また、投与期間にみられた腺胃粘膜の過形成は消失し、病変の回復性がみられた。

性	雄		非交配群	
投与量（mg/kg）	0	1000	0	1000
動物数	5	5	5	5
境界縁の扁平上皮過形成	0	2	0	1
軽微	0	0	0	1
軽度	0	2	0	0

【腎臓】

投与期間と同様に、尿細管の好酸性小体の増加が雄の 1000 mg/kg 投与群にみられた。本変化は回復動物に残存したものの、その程度及び頻度は軽減し、病変の回復性がみられた。

性	雄	
投与量（mg/kg）	0	1000
動物数	5	5
尿細管の好酸性小体の増加	0	1
軽微	0	1

【下部尿路系組織（膀胱及び尿道口周囲）】

投与期間と同様に、膀胱の移行上皮のびまん性過形成が、雄及び非交配群の 1000 mg/kg 投与群に残存したものの、その程度及び頻度は軽減し、非交配群では病変の回復性がみられた。

性	雄		非交配群	
投与量（mg/kg）	0	1000	0	1000
動物数	5	5	5	5
膀胱				
移行上皮のびまん性過形成	0	2	0	1
軽微	0	1	0	1
軽度	0	1	0	0

なお、非交配群の 1 例（動物番号 4121）において、膀胱に炎症性細胞浸潤を伴った移行上皮乳頭腫及び粘膜下の細胞浸潤（軽度）、膀胱腔内の好塩基性物質沈着（軽微）、外尿道口周囲組織に炎症（軽度）、尿道に扁平上皮のびまん性過形成（軽度）がみられ、尿路腔内には好塩基性物質（軽微）がみられた。

7.11　性周期（Table 11、Appendix 10-1~10-4）

発情期像発現回数、平均性周期日数及び性周期異常率では、対照群と各被験物質投与群との間に有意差は認められなかった。

なお、性周期異常が 40 及び 200 mg/kg 投与群の各 1 例（動物番号 2110 及び 3109）にみられた。動物番号 2110 は交尾したものの不妊であった。しかし、発現頻度に用量との関連はなく、偶発的変化と判断した。

7.12　交配成績（Table 12、Appendix 11-1~11-4）

交尾までに要した日数、交尾率、授精率及び受胎率では、対照群と各被験物質投与群との間に有意差は認められなかった。

なお、未交尾が 40 mg/kg 投与群で 1 組（動物番号 2112 と 2012）みられた。この相手雌は交配終了日を妊娠 0 日とみなし、妊娠 25 日に剖検したが、不妊であった。また、40 mg/kg 投与群で 2 組（動物番号 2109 と 2009、2110 と 2010）及び 200 mg/kg 投与群で 1 組(動物番号 3110 と 3010)は交尾したが、相手雌は不妊であった。しかし、高用量群の 1000 mg/kg の全ての組み合わせにおいて、交尾が成立し、相手雌は全例受胎したことから、用量との関連はなく、上記の未交尾及び交尾はしたが相手雌が不妊であった雌雄の発現は、被験物質投与との関連はないと判断した。

7.13　分娩成績（Table 13、Appendix 12-1~12-4）並びに分娩及び哺育状態（Table 1-5 及び 1-6、Appendix 1-17~1-24）

出産率、妊娠期間、黄体数、着床痕数、着床率、分娩率、死産児率、出生児数及び外表異常率に被験物質投与の影響は認められず、外表異常もみられなかった。

哺育状態では、いずれの母動物ともに児集め、営巣及び授乳行動に異常はなかった。

なお、平均着床痕数が全ての被験物質投与群で有意な高値を示し、出産児数が高値傾向を示した。これは対照群の値がわずかに低かったことによる偶発的変化である。また、200 mg/kg 投与群の着床率が有意な高値を示したが、用量に関連した変化ではなく、偶発的変化である。

7.14　出生児の生存率（Table 14、Appendix 13-1~13-4）

出生率及び生後 4 日生存率では、対照群と各被験物質投与群との間に有意差は認められなかった。

7.15　出生児の性比（Table 15、Appendix 14-1~14-4）

出産児並びに出生児の生後 0 及び 4 日の性比では、対照群と各被験物質投与群との間に有意差は認められなかった。

7.16　出生児の体重（Table 16、Appendix 15-1~15-4）

生後 0 及び 4 日の雌雄体重並びに生後 0~4 日の体重増加量では、対照群と各被験物質投与群との間に有意差は認められなかった。

7.17　死亡児の肉眼観察所見（Table 17、Appendix 16-1~16-4）

いずれの死亡児にも肉眼的異常はなかった。

7.18　出生児の生後 4 日肉眼観察所見（Table 18、Appendix 17-1~17-4）

いずれの出生児にも肉眼的異常はなかった。

8. 考察

リアクティブ ブラック-5 を注射用水で溶解し、40、200 及び 1000 mg/kg の投与量で Sprague-Dawley 系 SPF ラットの雄（12 匹/群）には交配前 14 日間に加え交配期間を通して剖検前日まで（42 日間）、雌（12 匹/群）には交配前 14 日間に加え交配期間及び妊娠期間を通して授乳 4 日まで（39~47 日間、全児死産動物を含む）、非交配群（対照群及び 1000 mg/kg 投与群：10 匹/群）には 42 日間強制経口投与し、反復投与毒性及び生殖発生毒性を検討した。更に、対照群及び 1000 mg/kg 投与群の一部の動物（雄及び非交配群の各群 5 匹）については、42 日間投与した後 14 日間の回復期間を設け、毒性変化の可逆性を検討した。なお、対照群には媒体である注射用水を投与した。

8.1 反復投与毒性

本被験物質はジアゾ構造をもった染料（カラーインデックス番号：C.I.20505）であり、木綿、毛織物、絹、ポリアミド織物を染色する色素として使用されている。被験物質は暗紫色の粉末であり、全ての被験物質投与群の投与液は暗紫色~黒色である。

各被験物質投与群で被験物質の色調の変化が排泄物（糞尿）、全身皮膚、精巣、腎臓及び肝臓にみられた。しかし、これら変化は回復終了時には消失あるいは軽減し、かつ皮膚（皮下組織を含む）、精巣、腎臓及び肝臓に着色に伴う組織変化はなく、毒性学的意義はないと判断した。また、非交配群の 1000 mg/kg 投与群の回復群の 1 例（動物番号 4121）において、膀胱の移行上皮乳頭腫を始めとした尿路系（膀胱及び尿道）の異常が観察された。膀胱の移行上皮乳頭腫は 19 週齢（剖検時）では極めて稀であること、同群の他の動物で軽度な粘膜上皮過形成が認められているものの、尿道口の腫脹は投与初期から 1 例のみにみられた変化であり、更に粘膜上皮過形成のグレード(軽度)から乳頭腫との間の所見のグレードに不連続性があることを考慮すると、本動物でみられた異常は被験物質投与による膀胱粘膜上皮過形成に加え、偶発的な膀胱結石及び尿路腔内の好塩基性物質が重なったことで種々の変化が惹起されたと考えられ、偶発的変化の可能性が高い。

雄及び非交配群の 1000 mg/kg 投与群でナトリウムの尿中排泄量が高値を示した。これに関連して、雄の 1000 mg/kg 投与群で血中カリウム及び塩素の低値と 200 及び 1000 mg/kg 投与群で腎臓の相対重量の高値、非交配群の 1000 mg/kg 投与群で塩素の低値と腎臓の絶対重量の高値、交配群雌の 1000 mg/kg 投与群で尿素窒素の高値と腎臓の絶対重量の高値が認められた。本変化は腎臓組織に異常がないことから、過剰投与された本被験物質中のナトリウム排泄による反応性変化と考えられるが、血中の電解質のアンバランスとごく軽微な尿素窒素の高値が生じたことから､毒性と判断した。これらは回復期間終了時に消失あるいは軽減したことから、可逆性の変化であった。なお、回復期間終了時にも非交配群の 1000 mg/kg 投与群でナトリウムの低値（対照群の 141 mmol/L に対し、140 mmol/L）が認められたが、ごく軽微な変化であり、投与期間終了時には認められないこと、塩素の低値は軽減していることから、偶発的変

化の可能性が高い。

雄の 1000 mg/kg 投与群でプロトロンビン時間の延長、非交配群の 1000 mg/kg 投与群でフィブリノーゲン量の低値が認められ、非交配群の同群で肝臓の相対重量の高値もみられた。しかし、生産を抑制する肝障害及び消費を亢進する DIC、出血、炎症等の異常がないことから、本変化の作用機序は明らかでない。同変化は回復期間終了時にみられず、可逆性の変化であった。

雄の 1000 mg/kg 投与群で総胆汁酸の高値が認められ、回復性もなかった。しかし、肝機能及び組織学的異常がみられないことから、本変化の作用機序は明らかでない。

雄の 1000 mg/kg 投与群で回復終了時に心臓の相対重量の高値（対照群の 0.31 g/100 g 体重に対し、0.29 g/100 g 体重、試験施設の背景データ、Mean±2S.D.：0.29 ± 0.05、n=75、2009/04~2013/03）が認められたが、相対重量のみの変化であり、背景データ内であること、組織学的に異常がないことから、被験物質との関連のない偶発的変化と判断した。

1000 mg/kg 投与群において、腺胃粘膜の過形成及び境界縁の扁平上皮細胞過形成が雄、交配群雌及び非交配群に、大腸粘膜のびまん性過形成が直腸で雄、交配群雌及び非交配群に、盲腸で雄及び非交配群に、結腸で雄に、膀胱で移行上皮のびまん性過形成が雄、交配群雌及び非交配群に認められた。これら変化は被験物質の刺激性との関連が疑われた。他に、200 mg/kg 以上の投与群の雄で抗 α2u グロブリン抗体の免疫染色で陽性を示す尿細管の好酸性小体の増加が認められたが、雄ラットにおける特異的変化であり、雌ラットや他の動物種ではみられない[7]。なお、本変化は回復期間終了時に軽減した。

その他の検査では、被験物質投与による影響は認められなかった。

8.2　生殖発生毒性

雌雄動物の各被験物質投与群でも被験物質投与の影響は認められず、雌雄動物の交尾能、授精能及び受胎能、母動物の妊娠維持、分娩及び哺育行動などの生殖機能への影響はないと判断した。また、各被験物質投与群においても児の子宮内発生、発育及び分化並びに生存性などへの影響はなかった。

これらの結果から、本試験条件下でリアクティブ　ブラック-5 を反復経口投与することにより、200 mg/kg 以上の投与群で腎臓（雄）、1000 mg/kg 投与群で腎臓及び肝臓（雌）、胃、直腸、盲腸及び膀胱（雌雄）、結腸（雄）に被験物質投与の影響が認められ、プロトロンビン時間の延長（雄）、総胆汁酸の高値（雄）及びフィブリノーゲン量の低値（雌）がみられた。雌雄親動物の生殖能力及び児動物には被験物質投与による影響は認められなかった。したがって、本被験物質の反復投与毒性に対する無影響量及び無毒性量は雄で 40 mg/kg、雌で 200 mg/kg と判断した。また、雌雄親動物の生殖能力に対する無影響量及び無毒性量は雌雄で 1000 mg/kg、児動物における無影響量及び無毒性量は 1000 mg/kg と判断した。

9. 文献

[1] [redacted]リアクティブ　ブラック-5 の IR を用いた特性試験並びに吸光光度法を用いた被験液（媒体：注射用水）中濃度測定法バリデーション及び安定性試験（株式会社ボゾリサーチセンター　御殿場研究所、試験番号：A-2543、2013 年）

[2] [redacted] リアクティブ　ブラック-5 のラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）（株式会社ボゾリサーチセンター、試験番号 : N-R040、2013 年）

[3] Snedecor GW, Cochran WG. Statistical methods. 8th ed. Ames: Iowa State University Press; 1989.

[4] Dunnett, CW. New tables for multiple comparisons with a control. Biometrics 1964; 20: 482-91.

[5] Steel RGD. A multiple comparison rank sum test: Treatments versus control. Biometrics 1959; 15: 560-72.

[6] 佐久間昭（1981）：薬効評価－計画と分析–II, pp.23-27, 387-389, 東京大学出版会, 東京.

[7] 伊東信行編著：III.標的器官の毒性病理（2）, 泌尿器系 C．腎臓, In：最新 毒性病理組織学, 名古屋, 中山書店, 東京，200 （1994）.

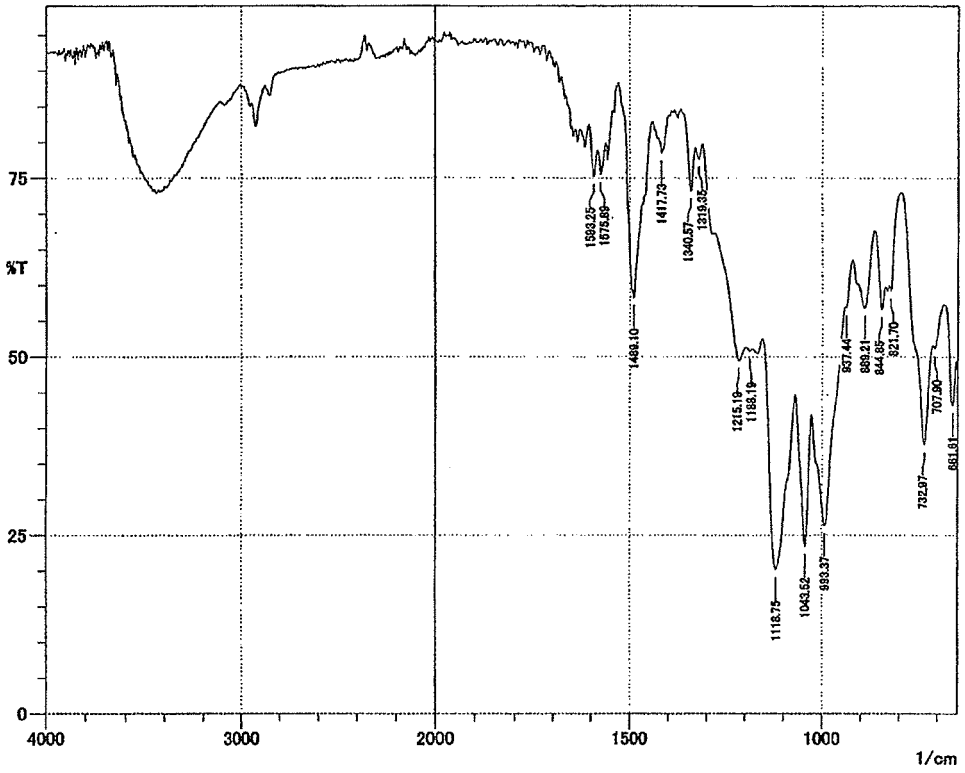
R-1114
添付資料　1

試験番号：A-2543

試験成績書
（リアクティブ　ブラック-5 の特性）

ステージ　：　被験物質の使用前
測定日　：　2013 年 6 月 3 日
被験物質　：　リアクティブ　ブラック-5
（ロット番号：15112DDV）
測定項目　：　赤外吸収スペクトル〔全反射測定法（ATR 法）〕

結果　：　特性のスペクトルを以下に示す。



基準　：　「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：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

[redacted]　2013 年 6 月 11 日

試験責任者
株式会社ボゾリサーチセンター　御殿場研究所

R-1114
添付資料　2 (1/2)

試験番号：R-1114

試験成績書
（被験物質の安定性）

ステージ	：	投与期間終了後
測定日	：	2013 年 10 月 28 日 2013 年　6 月　3 日　（特性のスペクトル[1)]）
被験物質	：	リアクティブ　ブラック-5 （ロット番号：15112DDV）
測定項目	：	赤外吸収スペクトル ［全反射測定法（ATR 法）］
判定基準	：	安定性のスペクトルを特性のスペクトル[1)]と比較するとき、同様な赤外吸収スペクトルである。 1) [redacted]：リアクティブ　ブラック-5 の IR を用いた特性試験並びに吸光光度法を用いた被験液（媒体：注射用水）中濃度測定法バリデーション及び安定性試験（株式会社ボゾリサーチセンター　御殿場研究所、試験番号：A-2543）
結果	：	安定性のスペクトルを特性のスペクトルと比較したとき、同様な赤外吸収スペクトルが得られた。なお、赤外吸収スペクトルは次のページに示す。
判定	：	適
基準	：	「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：薬食発 0331 第 8 号、平成 23･03･29 製局第 6 号、環保企発第 110331010 号）

[redacted]　2013 年 11 月 27 日

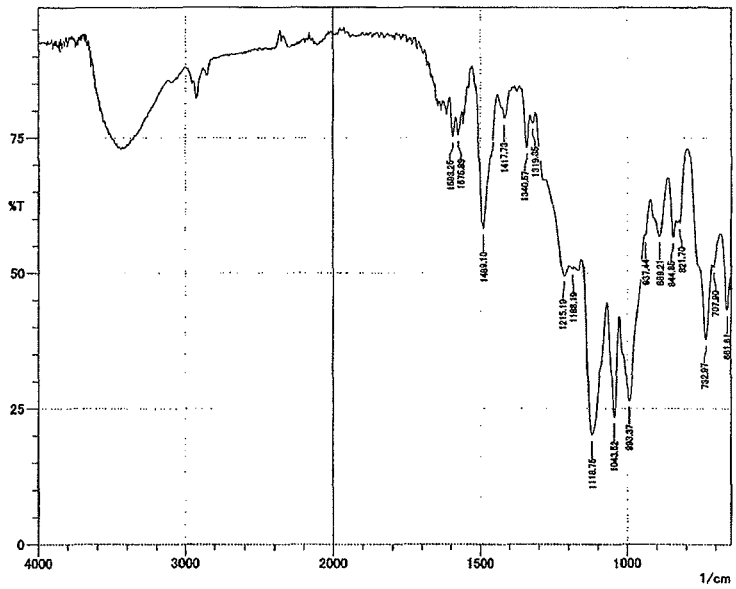
化学分析責任者
株式会社ボゾリサーチセンター　御殿場研究所

試験番号：R-1114

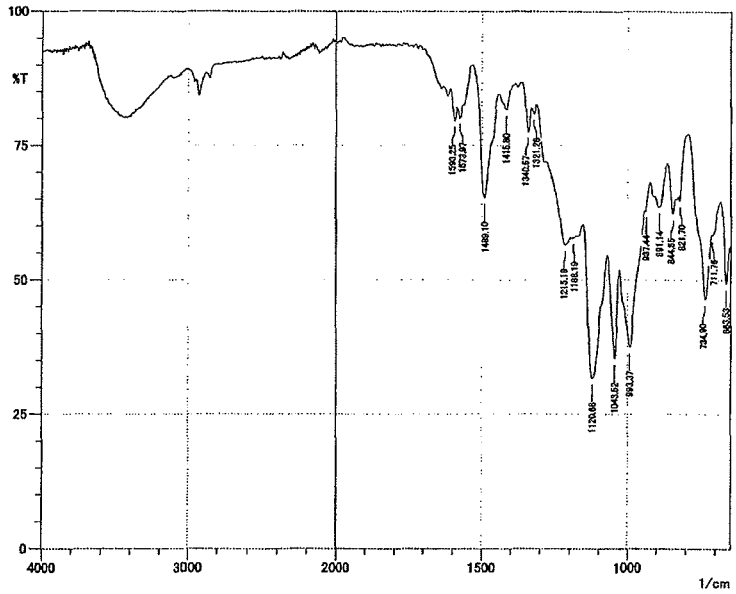
試験成績書
（被験物質の安定性）

結果　　：　赤外吸収スペクトル

（特性のスペクトル）



（安定性のスペクトル）



試験番号：A-2543

試験成績書
（被験液中リアクティブ　ブラック-5の安定性）

被験物質　：　リアクティブ　ブラック-5
（ロット番号：15112DDV、色素含量：55%）
形態（媒体）　：　溶液（注射用水）
保存条件　：　褐色ガラス瓶にて、冷所（冷蔵庫内、許容値：1~10°C）又は室温保存
保存期間　：　冷所で8日間保存した後、室温で24時間保存
評価基準
安定性　：　残存率｛調製直後の測定濃度の平均値（100）に対する保存後の測定濃度の平均値の割合｝が100.0±10.0%以内。

結果：

調製濃度[a)] (mg/mL)		測定濃度（mg/mL）	
		調製直後	冷所で8日間保存した後、室温で24時間保存後
1.00		1.01	1.02
		1.02	1.02
		1.02	1.02
	平均値	1.02	1.02
	残存率（%）	100	100.0
200		202	209
		205	209
		203	209
	平均値	203	209
	残存率（%）	100	103.0

[a)] 色素含量換算（換算係数：1.818）後の調製濃度

判定　：　適

基準　：　「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：薬食発0331第8号、平成23・03・29製局第6号、環保企発第110331010号）

[redacted]　2013年6月20日

試験責任者
株式会社ボゾリサーチセンター　御殿場研究所

R-1114
添付資料　4

分析結果

試験番号　：　R-1114
項目　：　濃度
ステージ　：　初回投与
分析日　：　2013 年 8 月 23 日

測定試料
　被験物質　：　リアクティブ　ブラック-5
　（ロット番号：15112DDV）
　形態　：　溶液
　媒体　：　注射用水
　調製日　：　2013 年 8 月 22 日

測定対象物質　：　リアクティブ　ブラック-5

評価基準
　濃度　：　表示値に対する割合；100.0±10%

結果：

表示値 (mg/mL)	測定濃度 (mg/mL)	平均値	表示値に対する割合 (%)
8	8.62 8.27 8.31	8.40	105.0
40	40.2 40.9 40.6	40.6	101.5
200	202 200 205	202	101.0

判定　：　適

R-1114
添付資料　5

分析結果

試験番号　：　R-1114
項目　：　濃度
ステージ　：　投与６週
分析日　：　2013年9月27日

測定試料
　被験物質　：　リアクティブ　ブラック-5
　（ロット番号：15112DDV）
　形態　：　溶液
　媒体　：　注射用水
　調製日　：　2013年9月27日

測定対象物質　：　リアクティブ　ブラック-5

評価基準
　濃度　：　表示値に対する割合；100.0±10%

結果：

表示値 (mg/mL)	測定濃度 (mg/mL)	平均値	表示値に対する割合 (%)
8	8.05 8.14 8.24	8.14	101.8
40	41.2 41.0 41.1	41.1	102.8
200	206 207 205	206	103.0

判定　：　適

R-1114
添付資料　6

リアクティブ　ブラック-5 のラットを用いた 14 日間反復経口投与毒性試験（投与量設定試験）における所見

試験番号：N-R040

被験物質		媒体[注]	リアクティブ　ブラック-5		
投与量(mg/kg)		0	100	300	1000
投与容量(mL/kg)		5	5	5	5
使用動物数(♂/♀)		5/5	5/5	5/5	5/5
死亡動物数(♂/♀)		0/0	0/0	0/0	0/0
一般状態		−	淡紫色尿（♂） （投与 2~9 日） 暗青色便（♂♀） （投与 2~15 日）	淡紫色尿（♂♀） （投与 2~15 日） 暗青色便（♂♀） （投与 2~15 日）	淡紫色尿（♂♀） （投与 1~15 日） 暗青色便（♂♀） （投与 2~15 日）
体重		−	−	↓：投与 10、14 日（♀）	↓：投与 10 日（♀）
摂餌量		−	−	−	−
血液学検査		−	MCV：↑（♀）	−	−
血液化学検査		−	−	−	総コレステロール：↑↑（♂）
器官重量	絶対	−	−	−	−
	相対	−	−	腎臓：↑（♀）	肺：↓（♂） 心臓：↑（♀） 腎臓：↑（♀）
剖検		−	脾臓：白色巣（♂1）	副腎：白色巣（♂1）	腎臓：黒色化（♂3♀5） 精巣：青色化（♂2） 全身皮下：青色化（♂3♀5） 顎下腺：青色化（♀1） 舌下腺：青色化（♀1） 膀胱：青色化（♀1） 子宮：青色化（♀2）

注：注射用水
−　：著変なし
/　：データなし又は判別不明あるいは検定不能
↑又は↓；$p<0.05$，↑↑又は↓↓；$p<0.01$，(対照群との間に有意差あり)

R-1114

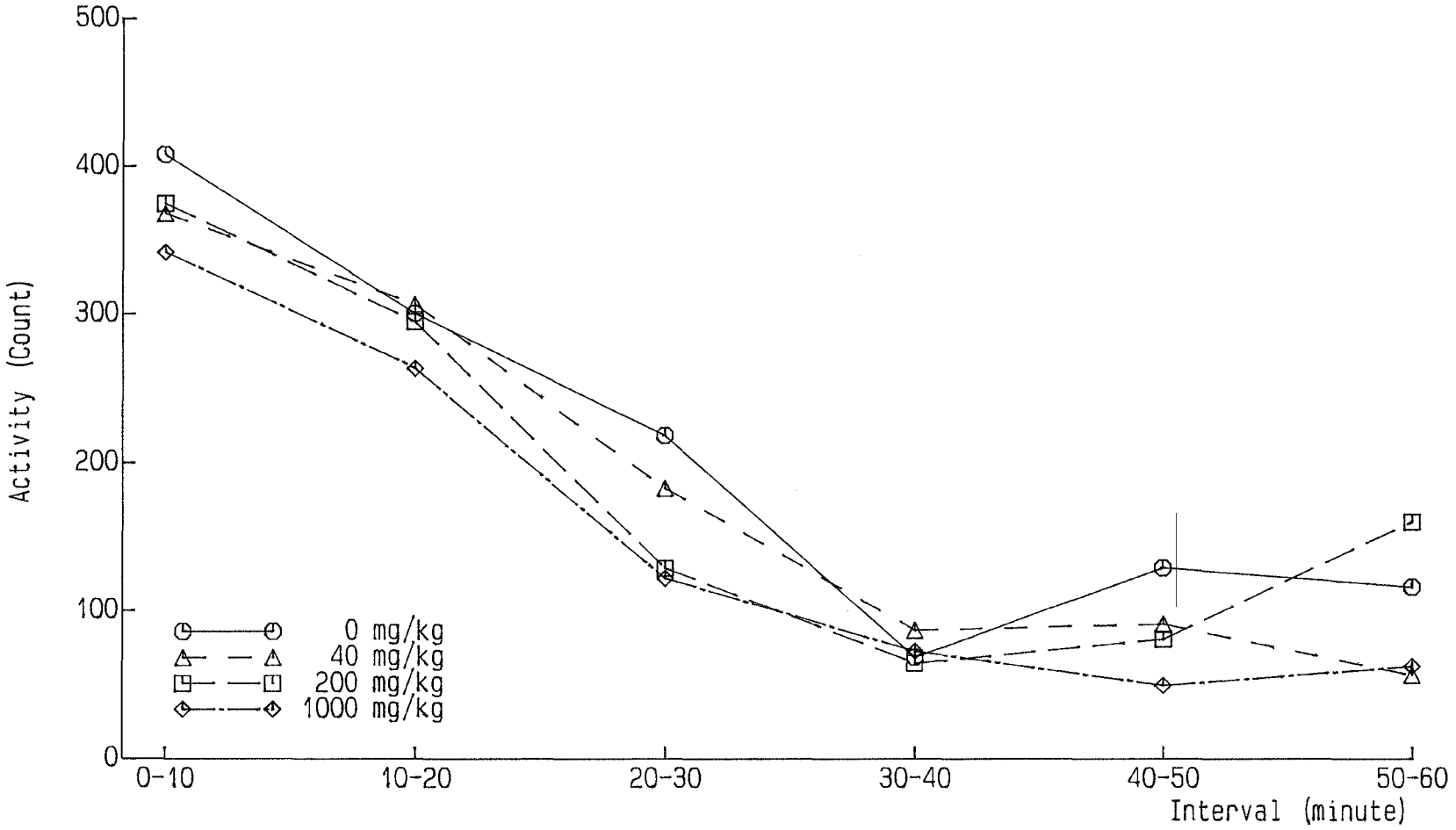


Fig.1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Motor activity of male rats (Week 6 of administration)

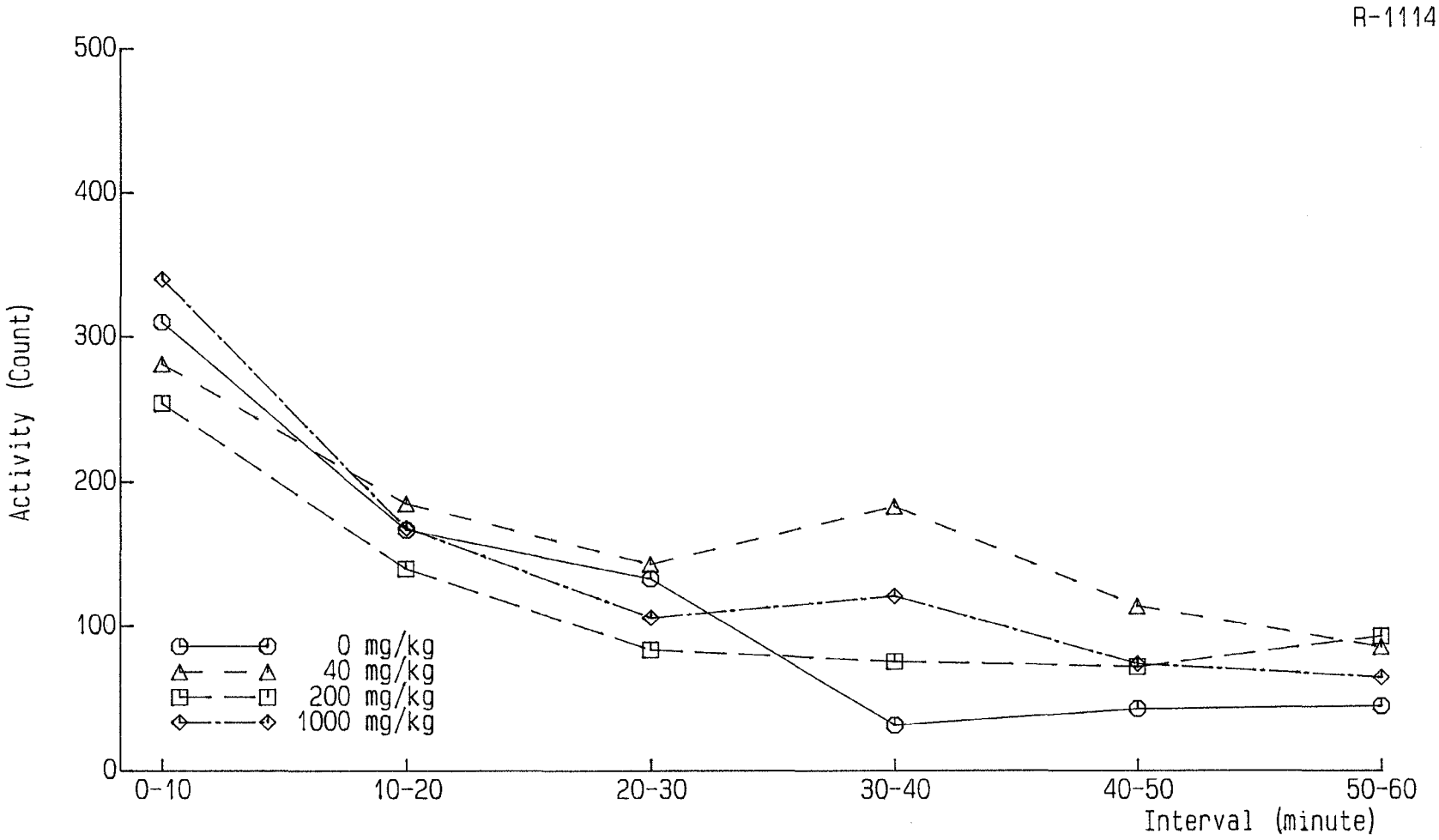


Fig.2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Motor activity of female rats (Main group, Lactation day 4)

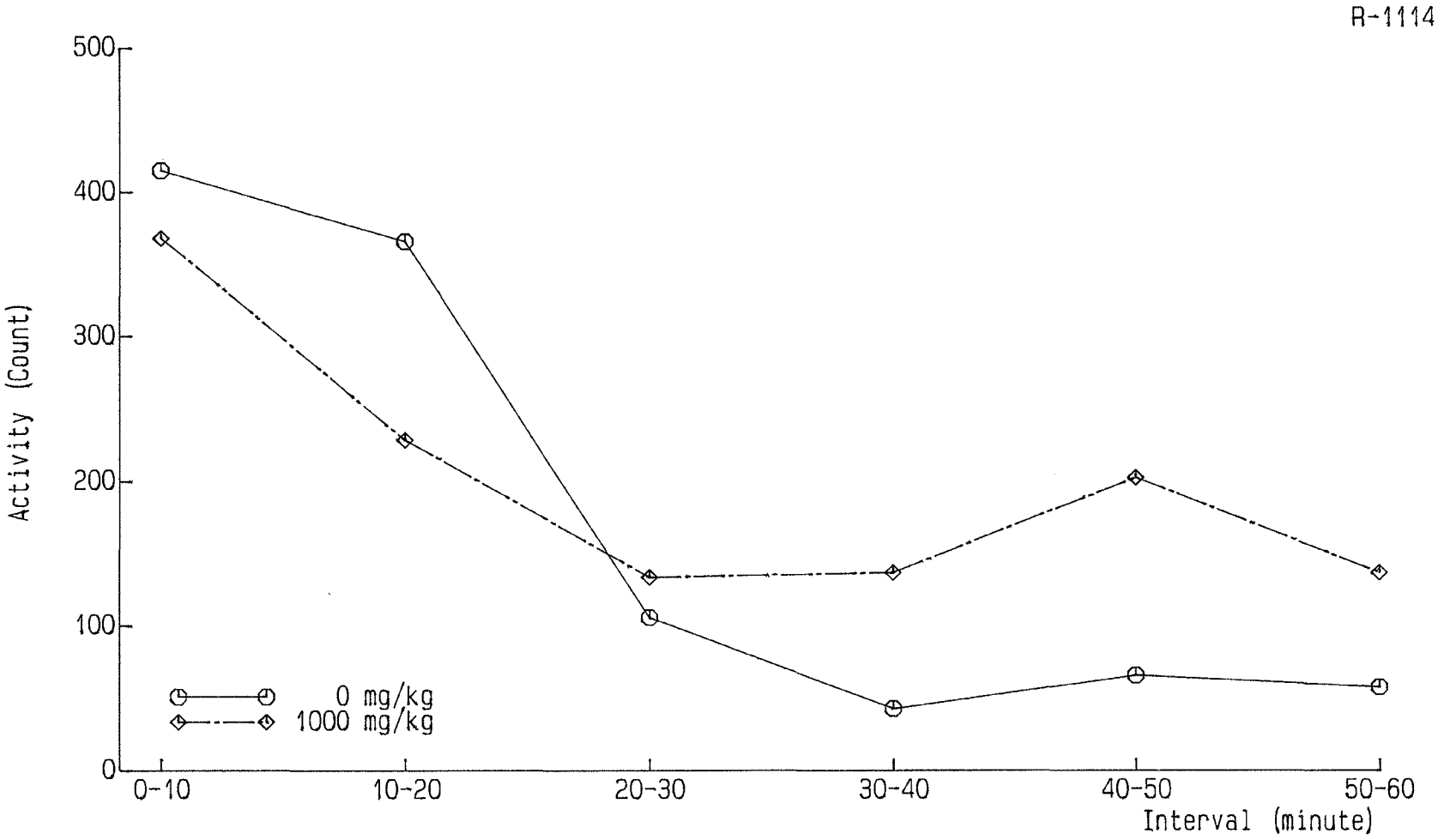


Fig.3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Motor activity of female rats (Satellite group, Week 6 of administration)

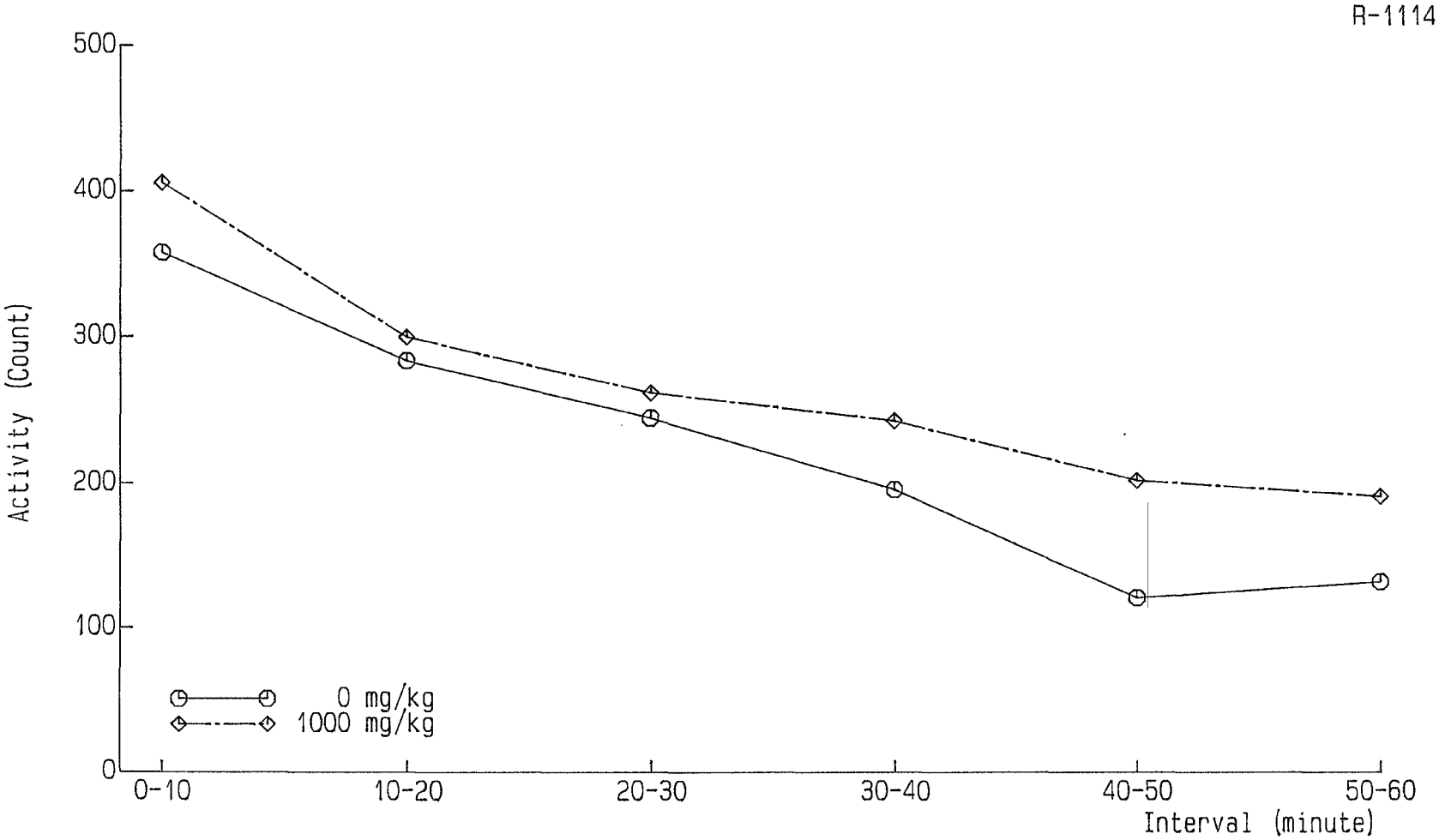


Fig.4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Motor activity of male rats (Week 2 of recovery)

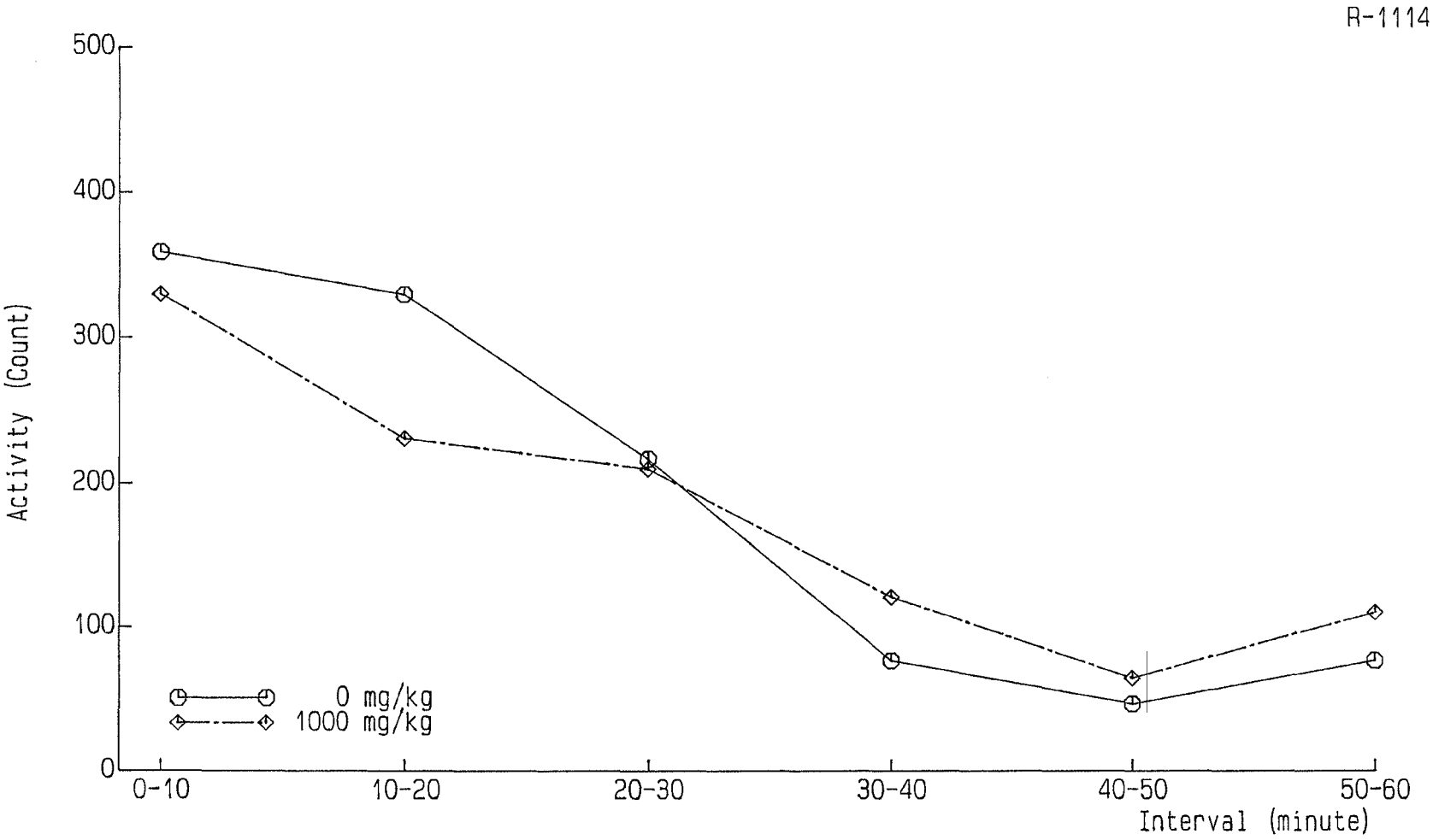


Fig.5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Motor activity of female rats (Week 2 of recovery)

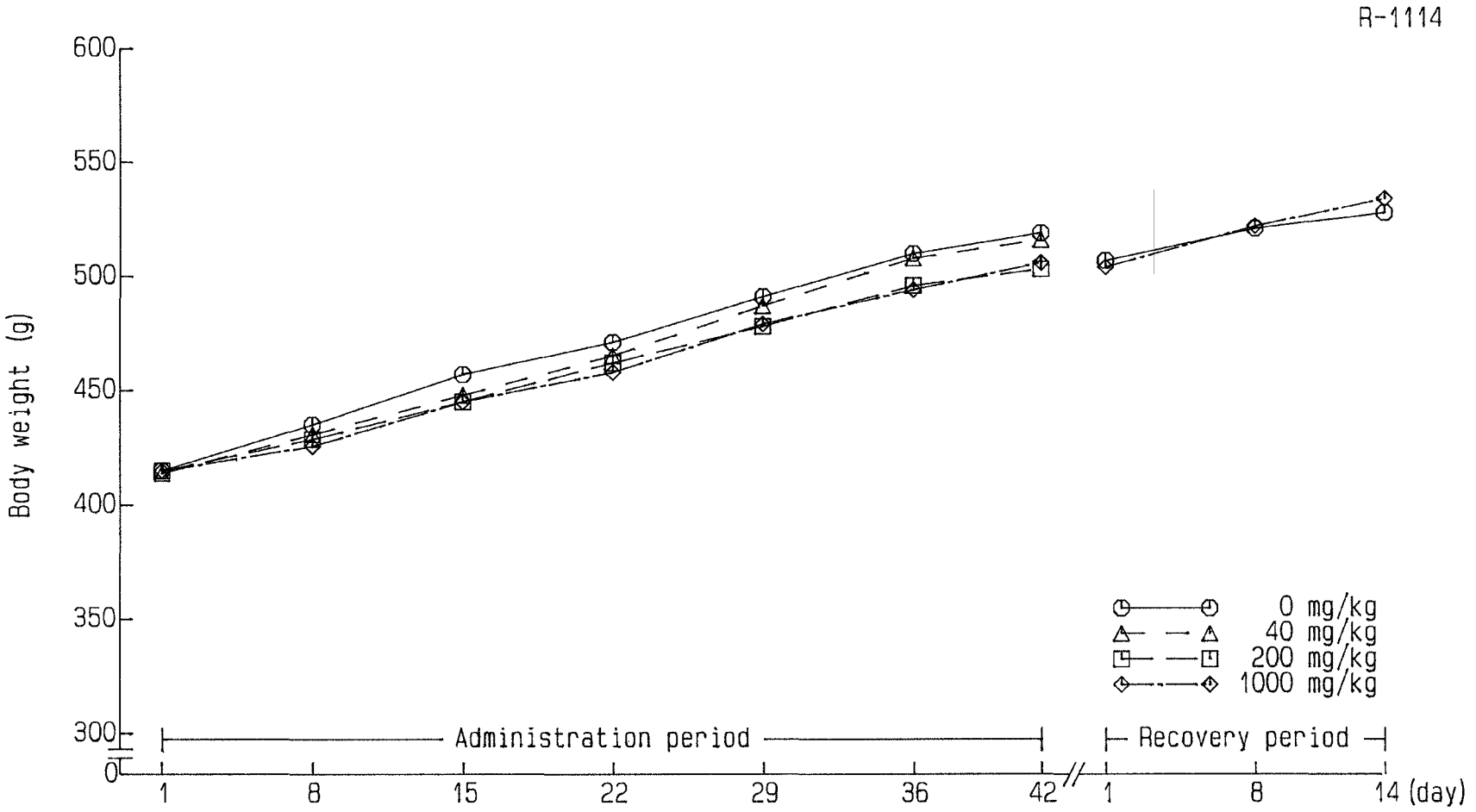


Fig.6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Body weight of male rats

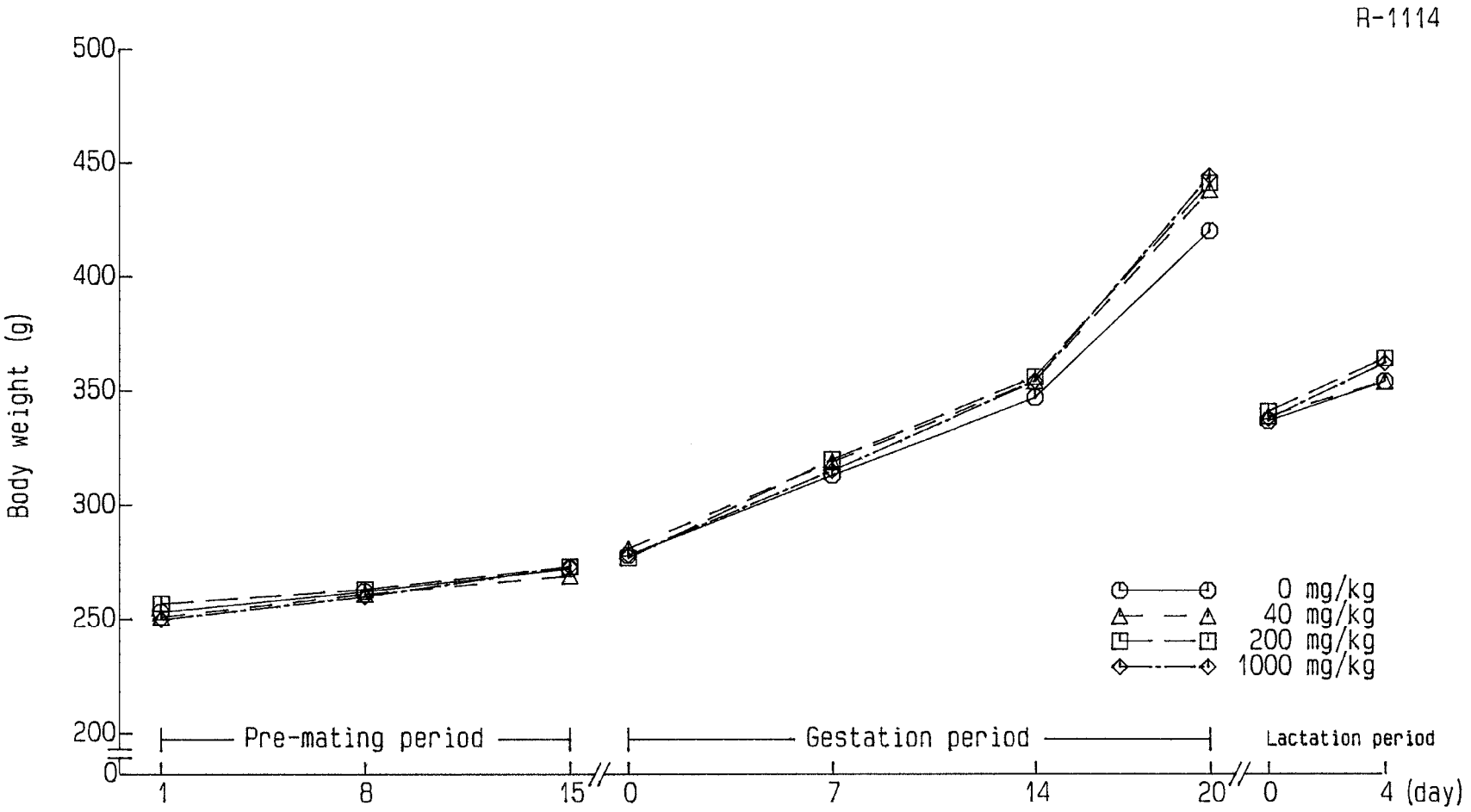


Fig.7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Body weight of female rats (Main group)

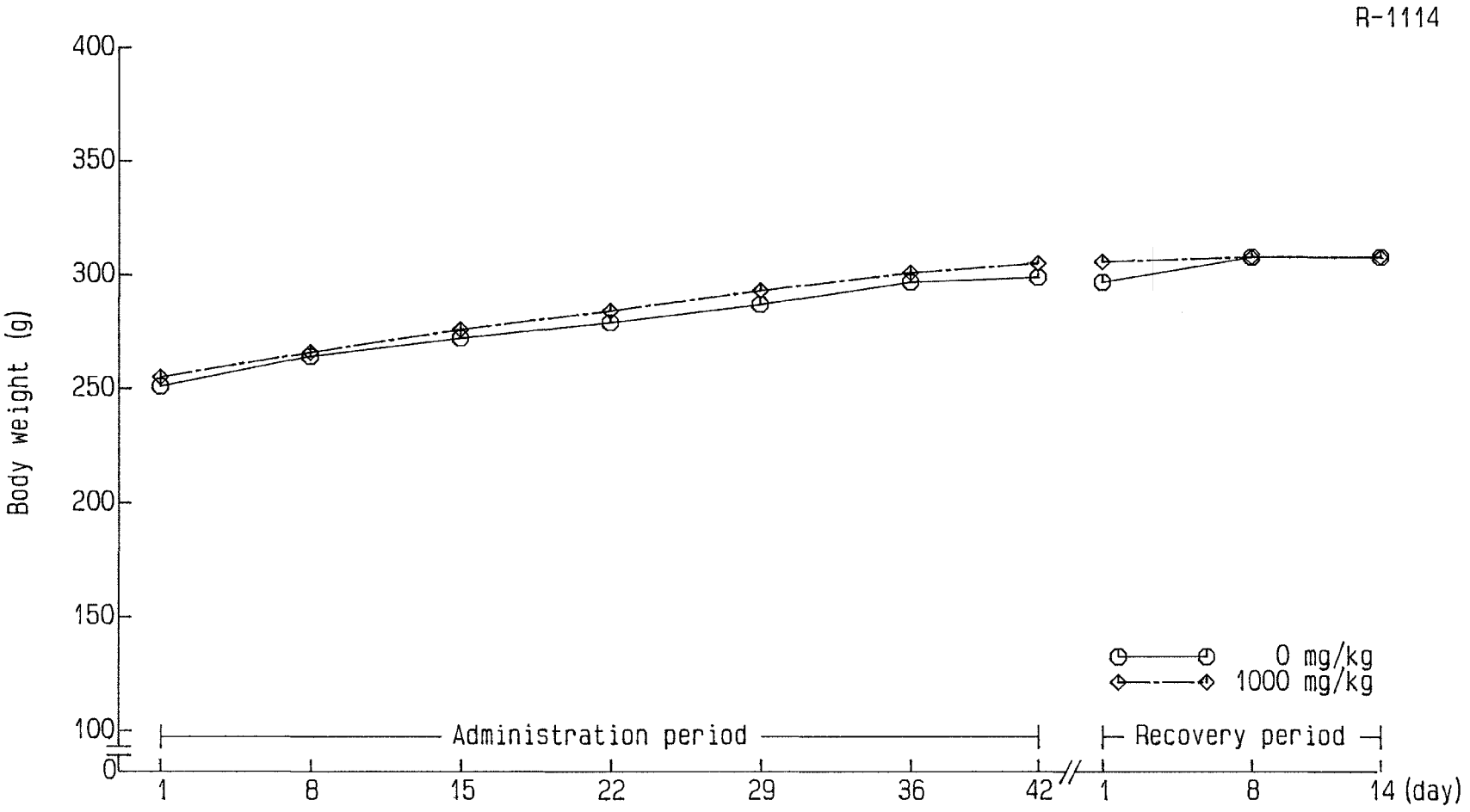


Fig.8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Body weight of female rats (Satellite group)

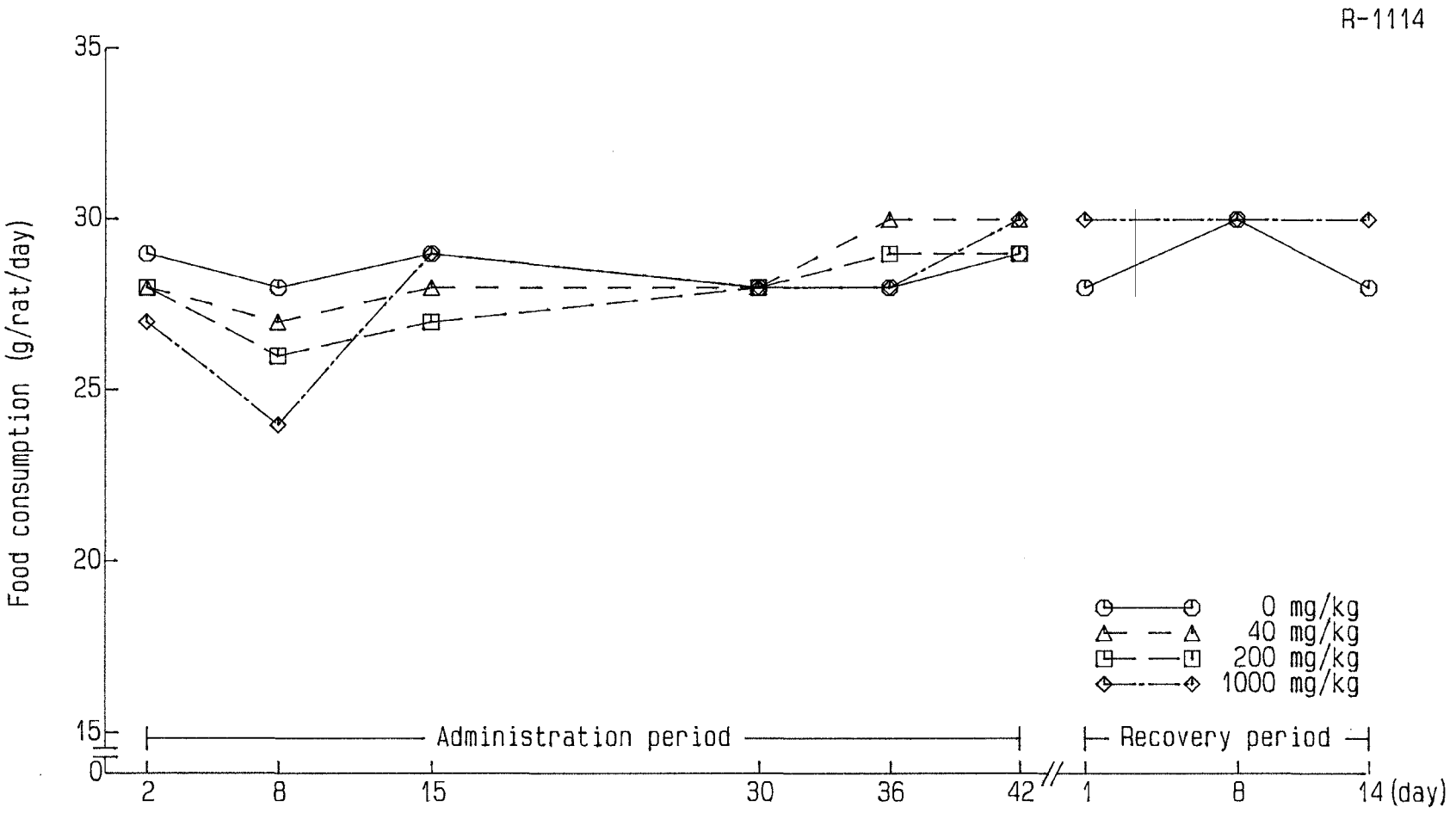


Fig.9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Food consumption of male rats

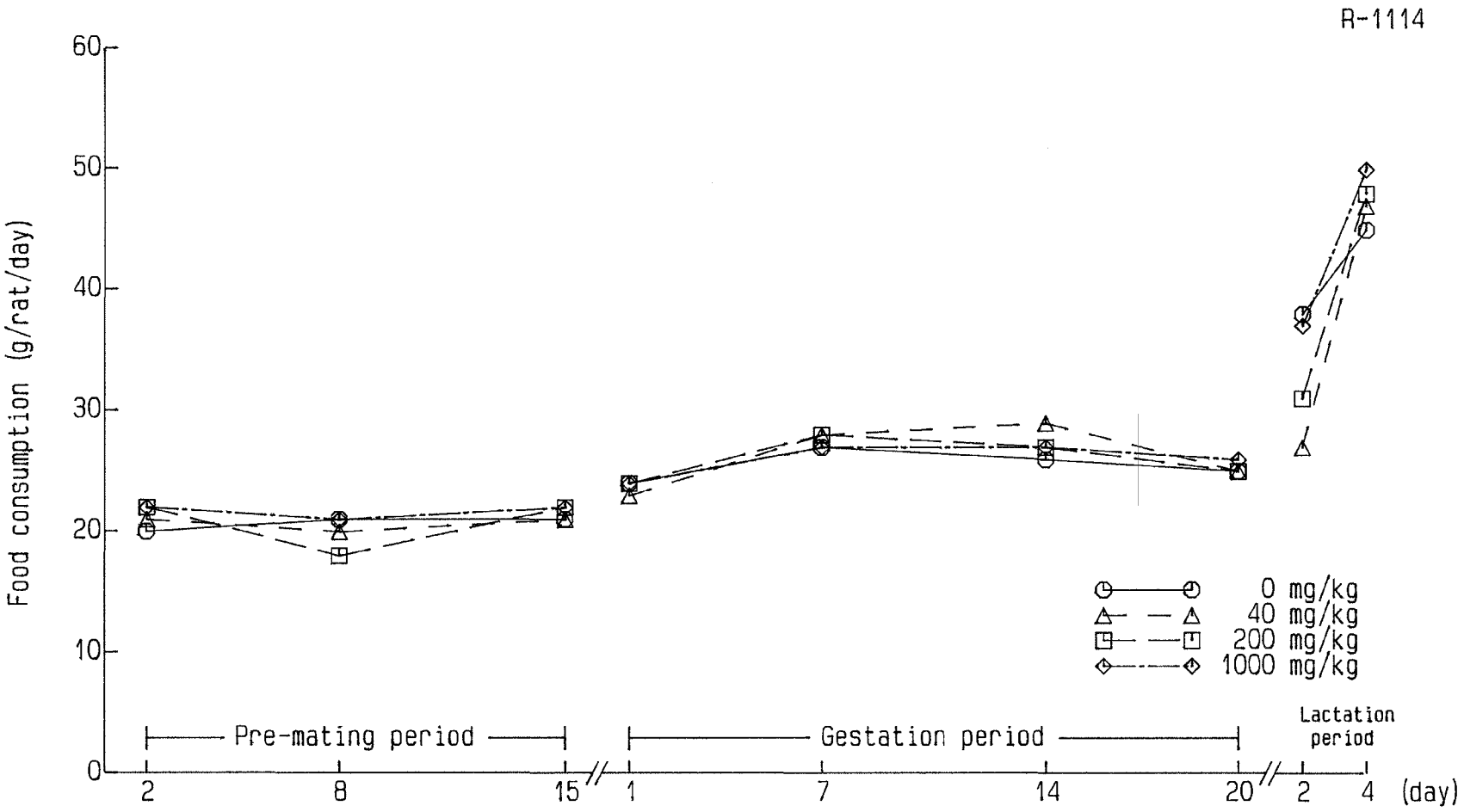


Fig.10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Food consumption of female rats (Main group)

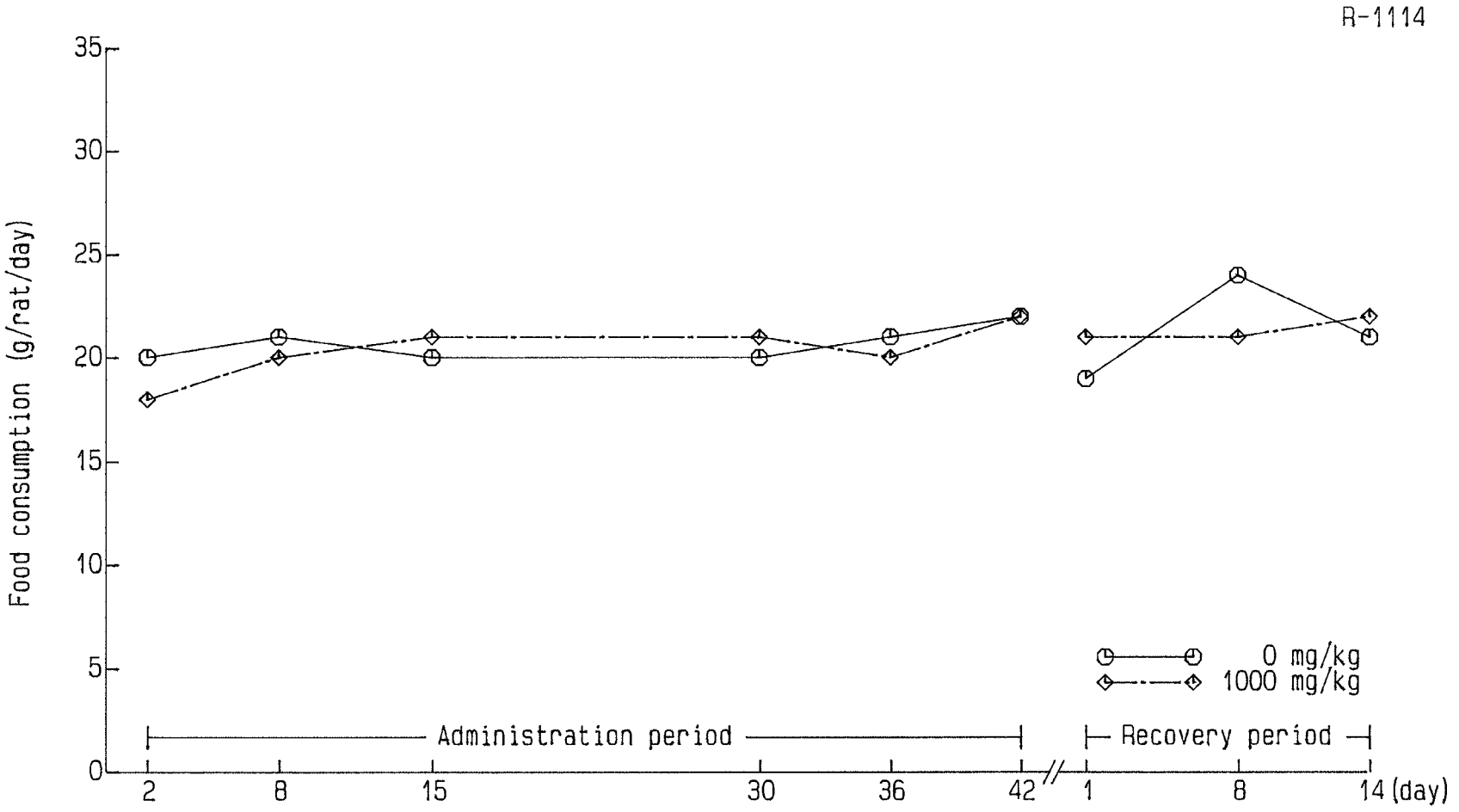


Fig.11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Food consumption of female rats (Satellite group)

Table 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	2	3	1	1	2	3	4	2	2	1	1	1
	Colored feces (dark blue)	0	0	2	3	1	1	2	3	4	2	2	1	1	1
200	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	12	12	12	12	12	12	12	12	12	12	12	12	12
	Colored feces (dark blue)	0	12	12	12	12	12	12	12	12	12	12	12	12	12
1000	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	4	12	12	12	12	12	12	12	12	12	12	12	12	12
	Colored urine (light purple)	4	4	2	1	3	2	1	2	3	2	2	1	3	2
	Colored feces (dark blue)	0	12	12	12	12	12	12	12	12	12	12	12	12	12
	Fracture of incisors	0	0	0	0	0	0	0	1	1	1	1	1	1	1

Table 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	1	0	0	0	1	1	1	0	1	0	0	0	0	0
	Colored feces (dark blue)	1	0	0	0	1	1	1	0	1	0	0	0	0	0
200	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	12	0	5	8	10	12	12	12	12	12	12	12	12	12
	Colored feces (dark blue)	12	0	5	8	10	12	12	12	12	12	12	12	12	12
1000	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	12	1	7	9	9	11	11	12	12	12	12	12	12	12
	Colored urine (light purple)	3	0	0	0	0	0	1	4	3	1	1	1	2	2
	Colored feces (dark blue)	12	0	6	9	9	11	11	12	12	12	12	12	12	12
	Fracture of incisors	1	1	1	1	0	0	0	0	0	0	0	0	0	0

Table 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in male rats (Administration period)

Dose mg/kg	Signs	Day of administration														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	2	3	0	1	1	2	0	1
	Colored feces (dark blue)	0	0	0	0	0	0	0	2	3	0	1	1	2	0	1
200	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Colored feces (dark blue)	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
1000	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	No. of animals with abnormal findings	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	Colored urine (light purple)	3	2	4	3	3	1	4	4	2	1	1	2	2	3	4
	Colored feces (dark blue)	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7

a): Day of necropsy

Table 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in female rats during the pre-mating period (Main group)

Dose mg/kg	Signs	Day of administration														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	1	1	1	0	0	3	3	2	1	1	0	0	0
	Colored feces (dark blue)	0	0	1	1	1	0	0	3	3	2	1	1	0	0	0
200	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Colored feces (dark blue)	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12
1000	No. of animals	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No. of animals with abnormal findings	4	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Colored urine (light purple)	4	1	1	1	1	0	2	3	1	2	3	1	0	0	3
	Colored feces (dark blue)	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Table 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in dams during the gestation period (Main group)

Dose mg/kg	Signs	Administration																								
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)
0	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	4	1	0
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	Continuation of delivery	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
40	No. of dams	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	2	0	
	No. of dams with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
200	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	0	
	No. of dams with abnormal findings	0	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1		
	Colored feces (dark blue)	0	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1		
1000	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	0		
	No. of dams with abnormal findings	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11			
	Colored urine (light purple)	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Colored feces (dark blue)	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11			

a): Gestation day

Table 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in dams during the lactation period (Main group)

Dose mg/kg	Signs	Administration 0	1	2	3	4a)	5b)
0	No. of dams	12	11c)	11	11	11	11
	No. of dams with abnormal findings	1	0	0	0	0	0
	Vaginal prolapse	1	0	0	0	0	0
40	No. of dams	9	9	9	9	9	9
	No. of dams with abnormal findings	0	1	1	1	1	1
	Colored feces (dark blue)	0	1	1	1	1	1
200	No. of dams	11	11	11	11	11	11
	No. of dams with abnormal findings	11	11	11	11	11	11
	Colored feces (dark blue)	11	11	11	11	11	11
1000	No. of dams	12	12	12	12	12	12
	No. of dams with abnormal findings	12	12	12	12	12	12
	Colored feces (dark blue)	12	12	12	12	12	12

a): Lactation day
b): Day of necropsy
c): One dam was necropsied on lactation day 0 because all pups were stillborn.

Table 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	1	10	10	10	10	10	10	10	10	10	10	10	10	10
	Colored urine (light purple)	1	2	0	3	0	0	0	0	0	1	0	1	0	0
	Colored feces (dark blue)	0	10	10	10	10	10	10	10	10	10	10	10	10	10
	Swelling, around the urethral orifice	0	0	0	0	0	0	0	1	1	1	1	1	1	1

Table 1-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration													
		15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	No. of animals with abnormal findings	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Colored urine (light purple)	1	0	2	1	0	0	0	2	1	0	1	0	0	2
	Colored feces (dark blue)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Swelling, around the urethral orifice	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 1-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in female rats (Satellite group, Administration period)

Dose mg/kg	Signs	Day of administration														
		29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
0	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	No. of animals with abnormal findings	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	Colored urine (light purple)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	Colored feces (dark blue)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	Swelling, around the urethral orifice	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
	Discoloration of skin, blue, systemic	0	0	0	0	2	2	3	3	3	3	3	3	3	3	0

a): Day of necropsy

Table 1-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in male rats (Recovery period)

Dose mg/kg	Signs	Day of recovery 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
0	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	5	3	0	0	0	0	0	0	0	0	0	0	0	0	0
	Colored urine (light purple)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Colored feces (dark blue)	5	3	0	0	0	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 1-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Clinical signs in female rats (Recovery period)

Dose mg/kg	Signs	Day of recovery 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
0	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000	No. of animals	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No. of animals with abnormal findings	5	4	4	2	2	1	1	1	1	1	1	1	1	1	1
	Colored urine (light purple)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Colored feces (dark blue)	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Swelling, around the urethral orifice	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Discoloration of skin, blue, systemic	3	3	3	1	1	0	0	0	0	0	0	0	0	0	0

a): Day of necropsy

Table 2-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Posture					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12

Table 2-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Posture					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12

Table 2-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Posture					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12

Table 2-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Posture					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12

Table 2-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	11	9	11	12
Posture					
Normal		11	9	11	12
Convulsion					
None		11	9	11	12
Abnormal behavior					
None		11	9	11	12

Table 2-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Posture			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10

Table 2-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: home cage observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: home cage observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		10	11	10	10
Soft		2	1	2	2
Reactivity to handling					
Easy		12	12	12	12

Table 2-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	11
Some resistance/avoidance		0	0	0	1
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	11
Soft		0	0	0	1
Reactivity to handling					
Easy		12	12	12	11
Slightly awkward		0	0	0	1

Table 2-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		11	12	12	12
Soft		1	0	0	0
Reactivity to handling					
Easy		12	12	12	12

Table 2-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Ease of removal from cage					
Easy		12	12	12	12
Fur condition					
Normal		12	12	12	12
Skin					
Normal		12	12	12	12
Secretions-Eye, Nose					
Absent		12	12	12	12
Exophthalmos					
Absent		12	12	12	12
Palpebral closure					
Normal		12	12	12	12
Mucosal membranes					
Normal		12	12	12	12
Lacrimation					
Normal		12	12	12	12
Piloerection					
Absent		12	12	12	12
Pupil size					
Normal		12	12	12	12
Salivation					
None		12	12	12	12
Abnormal respiration					
Absent		12	12	12	12
Vocalization					
None		12	12	12	12
Reactivity to handling					
Easy		12	12	12	12

Table 2-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Ease of removal from cage					
Easy		12	9	11	12
Fur condition					
Normal		12	9	11	12
Skin					
Normal		12	9	11	12
Secretions-Eye, Nose					
Absent		12	9	11	12
Exophthalmos					
Absent		12	9	11	12
Palpebral closure					
Normal		12	9	11	12
Mucosal membranes					
Normal		12	9	11	12
Lacrimation					
Normal		12	9	11	12
Piloerection					
Absent		12	9	11	12
Pupil size					
Normal		12	9	11	12
Salivation					
None		12	9	11	12
Abnormal respiration					
Absent		12	9	11	12
Vocalization					
None		12	9	10	11
Soft		0	0	1	0
Moderate		0	0	0	1
Reactivity to handling					
Easy		12	9	11	12

Table 2-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Ease of removal from cage					
Easy		12	9	11	12
Fur condition					
Normal		12	9	11	12
Skin					
Normal		12	9	11	12
Secretions-Eye, Nose					
Absent		12	9	11	12
Exophthalmos					
Absent		12	9	11	12
Palpebral closure					
Normal		12	9	11	12
Mucosal membranes					
Normal		12	9	11	12
Lacrimation					
Normal		12	9	11	12
Piloerection					
Absent		12	9	11	12
Pupil size					
Normal		12	9	11	12
Salivation					
None		12	9	11	12
Abnormal respiration					
Absent		12	9	11	12
Vocalization					
None		12	9	11	11
Soft		0	0	0	1
Reactivity to handling					
Easy		12	9	11	12

Table 2-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Ease of removal from cage					
Easy		12	9	11	12
Fur condition					
Normal		12	9	11	12
Skin					
Normal		12	9	11	12
Secretions-Eye, Nose					
Absent		12	9	11	12
Exophthalmos					
Absent		12	9	11	12
Palpebral closure					
Normal		12	9	11	12
Mucosal membranes					
Normal		12	9	11	12
Lacrimation					
Normal		12	9	11	12
Piloerection					
Absent		12	9	11	12
Pupil size					
Normal		12	9	11	12
Salivation					
None		12	9	11	12
Abnormal respiration					
Absent		12	9	11	12
Vocalization					
None		12	9	11	12
Reactivity to handling					
Easy		12	9	11	12

Table 2-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Ease of removal from cage					
Easy		12	9	11	12
Fur condition					
Normal		12	9	11	12
Skin					
Normal		12	9	11	12
Secretions-Eye, Nose					
Absent		12	9	11	12
Exophthalmos					
Absent		12	9	11	12
Palpebral closure					
Normal		12	9	11	12
Mucosal membranes					
Normal		12	9	11	12
Lacrimation					
Normal		12	9	11	12
Piloerection					
Absent		12	9	11	12
Pupil size					
Normal		12	9	11	12
Salivation					
None		12	9	11	12
Abnormal respiration					
Absent		12	9	11	12
Vocalization					
None		12	9	11	12
Reactivity to handling					
Easy		12	9	11	12

Table 2-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	11	9	11	12
Ease of removal from cage					
Easy		11	9	11	12
Fur condition					
Normal		11	9	11	12
Skin					
Normal		11	9	11	12
Secretions-Eye, Nose					
Absent		11	9	11	12
Exophthalmos					
Absent		11	9	11	12
Palpebral closure					
Normal		11	9	11	12
Mucosal membranes					
Normal		11	9	11	12
Lacrimation					
Normal		11	9	11	12
Piloerection					
Absent		11	9	11	12
Pupil size					
Normal		11	9	11	12
Salivation					
None		11	9	11	12
Abnormal respiration					
Absent		11	9	11	12
Vocalization					
None		11	9	11	12
Reactivity to handling					
Easy		11	9	11	12

Table 2-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

Table 2-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

Table 2-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

Table 2-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		8	7
Soft		2	3
Reactivity to handling			
Easy		10	10

Table 2-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	10
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

Table 2-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Ease of removal from cage			
Easy		10	10
Fur condition			
Normal		10	10
Skin			
Normal		10	7
Slight		0	3a)
Secretions-Eye, Nose			
Absent		10	10
Exophthalmos			
Absent		10	10
Palpebral closure			
Normal		10	10
Mucosal membranes			
Normal		10	10
Lacrimation			
Normal		10	10
Piloerection			
Absent		10	10
Pupil size			
Normal		10	10
Salivation			
None		10	10
Abnormal respiration			
Absent		10	10
Vocalization			
None		10	10
Reactivity to handling			
Easy		10	10

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Table 2-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: in-the-hand observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	2
Slight		0	3a)
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

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Table 2-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: in-the-hand observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Ease of removal from cage			
Easy		5	5
Fur condition			
Normal		5	5
Skin			
Normal		5	5
Secretions-Eye, Nose			
Absent		5	5
Exophthalmos			
Absent		5	5
Palpebral closure			
Normal		5	5
Mucosal membranes			
Normal		5	5
Lacrimation			
Normal		5	5
Piloerection			
Absent		5	5
Pupil size			
Normal		5	5
Salivation			
None		5	5
Abnormal respiration			
Absent		5	5
Vocalization			
None		5	5
Reactivity to handling			
Easy		5	5

Table 2-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		3± 2	2± 2	3± 2	3± 2
Defecation count (Mean±S.D.)		0± 1	0± 0	0± 0	0± 1
Urination					
None		10	11	12	9
Small amount		2	1	0	3

No significant difference in any treated groups from control group.

Table 2-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		0	1	0	3
Normal		12	11	12	9
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		3± 3	2± 1	3± 1	2± 2
Defecation count (Mean±S.D.)		0± 0	0± 1	0± 0	0± 1
Urination					
None		10	12	10	12
Small amount		1	0	2	0
Moderate amount		1	0	0	0

No significant difference in any treated groups from control group.

Table 2-49 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 3 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		0	1	0	1
Normal		12	11	12	11
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		2± 2	2± 2	4± 2	2± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 1
Urination					
None		10	11	11	10
Small amount		1	1	1	1
Moderate amount		1	0	0	1

No significant difference in any treated groups from control group.

Table 2-50 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 4 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		3± 1	3± 2	3± 1	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		9	12	10	9
Small amount		3	0	2	3

No significant difference in any treated groups from control group.

Table 2-51 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 5 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		2	1	0	0
Normal		10	11	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		3± 2	3± 2	5± 1	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		10	11	11	11
Small amount		2	1	1	1

No significant difference in any treated groups from control group.

Table 2-52 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 6 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
No/minimal location		1	0	0	0
Normal		11	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		4± 2	3± 1	4± 2	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		10	12	10	10
Small amount		2	0	2	2

No significant difference in any treated groups from control group.

Table 2-53 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		7± 2	7± 3	6± 2	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		10	12	12	11
Small amount		2	0	0	1

No significant difference in any treated groups from control group.

Table 2-54 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	12	12	12
Arousal					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12
Stereotypy					
None		12	12	12	12
Gait					
Normal		12	12	12	12
Posture					
Normal		12	12	12	12
Grooming					
None		12	12	12	12
Rearing (Mean±S.D.)		7± 3	8± 2	7± 3	6± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	12	12	12

No significant difference in any treated groups from control group.

Table 2-55 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 1)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Arousal					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12
Stereotypy					
None		12	9	11	12
Gait					
Normal		12	9	11	12
Posture					
Normal		12	9	11	12
Grooming					
None		12	9	11	12
Rearing (Mean±S.D.)		7± 3	6± 2	6± 2	7± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	8	10	11
Small amount		0	1	1	1

No significant difference in any treated groups from control group.

Table 2-56 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 7)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Arousal					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12
Stereotypy					
None		12	9	11	12
Gait					
Normal		12	9	11	12
Posture					
Normal		12	9	11	12
Grooming					
None		12	9	11	12
Rearing (Mean±S.D.)		7± 2	7± 3	6± 2	7± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	9	9	11
Small amount		0	0	2	1

No significant difference in any treated groups from control group.

Table 2-57 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 14)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Arousal					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12
Stereotypy					
None		12	9	11	12
Gait					
Normal		12	9	11	12
Posture					
Normal		12	9	11	12
Grooming					
None		12	9	11	12
Rearing (Mean±S.D.)		7± 3	8± 5	6± 2	6± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		12	9	11	12

No significant difference in any treated groups from control group.

Table 2-58 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Gestation day 20)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	12	9	11	12
Arousal					
Normal		12	9	11	12
Convulsion					
None		12	9	11	12
Abnormal behavior					
None		12	9	11	12
Stereotypy					
None		12	9	11	12
Gait					
Normal		12	9	11	12
Posture					
Normal		12	9	11	12
Grooming					
None		12	9	11	12
Rearing (Mean±S.D.)		5± 2	5± 2	5± 2	5± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	9	11	11
Small amount		1	0	0	1

No significant difference in any treated groups from control group.

Table 2-59 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	11	9	11	12
Arousal					
Normal		11	9	11	12
Convulsion					
None		11	9	11	12
Abnormal behavior					
None		11	9	11	12
Stereotypy					
None		11	9	11	12
Gait					
Normal		11	9	11	12
Posture					
Normal		11	9	11	12
Grooming					
None		11	9	11	12
Rearing (Mean±S.D.)		7± 3	8± 2	6± 2	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 1	0± 0
Urination					
None		11	9	11	12

No significant difference in any treated groups from control group.

Table 2-60 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 1 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		6± 2	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	10

No significant difference between treated group and control group.

Table 2-61 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		6± 2	6± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	10

No significant difference between treated group and control group.

Table 2-62 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 3 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		7± 3	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		9	8
Small amount		1	2

No significant difference between treated group and control group.

Table 2-63 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		7± 2	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		9	8
Small amount		1	2

No significant difference between treated group and control group.

Table 2-64 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		8± 3	9± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		9	7
Small amount		1	3

No significant difference between treated group and control group.

Table 2-65 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	10	10
Arousal			
Normal		10	10
Convulsion			
None		10	10
Abnormal behavior			
None		10	10
Stereotypy			
None		10	10
Gait			
Normal		10	10
Posture			
Normal		10	10
Grooming			
None		10	10
Rearing (Mean±S.D.)		8± 3	10± 4
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		10	8
Small amount		0	2

No significant difference between treated group and control group.

Table 2-66 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		3± 0	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		4	4
Small amount		1	1

No significant difference between treated group and control group.

Table 2-67 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in male rats: open field observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		2± 1	2± 2
Defecation count (Mean±S.D.)		0± 0	0± 1
Urination			
None		5	4
Small amount		0	1

No significant difference between treated group and control group.

Table 2-68 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Week 1 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		7± 3	7± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-69 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Detailed clinical signs in female rats: open field observation (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Arousal			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5
Stereotypy			
None		5	5
Gait			
Normal		5	5
Posture			
Normal		5	5
Grooming			
None		5	5
Rearing (Mean±S.D.)		5± 2	5± 4
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-70 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Manipulative test of male rats (Week 6 of administration)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	5	5	5	5
Auditory response					
Normal		5	5	5	5
Approach response					
Normal		5	5	5	5
Touch response					
Normal		5	5	5	5
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		65±17	56±10	61± 9	65±31

No significant difference in any treated groups from control group.

Table 2-71 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Manipulative test of female rats (Main group, Lactation day 4)

Parameter	Dose (mg/kg)	0	40	200	1000
	No. of animals	5	5	5	5
Auditory response					
Normal		5	5	5	5
Approach response					
Normal		5	5	5	5
Touch response					
Normal		5	5	5	5
Tail pinch response					
Normal		5	5	5	5
Pupillary reflex					
Pass, both		5	5	5	5
Aerial righting reflex					
(Total score: Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		58±17	55±10	66±19	64±17

No significant difference in any treated groups from control group.

Table 2-72 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Manipulative test of female rats (Satellite group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		63±16	60±18

No significant difference between treated group and control group.

Table 2-73 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Manipulative test of male rats (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		52± 9	74±22

No significant difference between treated group and control group.

Table 2-74 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Manipulative test of female rats (Week 2 of recovery)

Parameter	Dose (mg/kg)	0	1000
	No. of animals	5	5
Auditory response			
Normal		5	5
Approach response			
Normal		5	5
Touch response			
Normal		5	5
Tail pinch response			
Normal		5	5
Pupillary reflex			
Pass, both		5	5
Aerial righting reflex			
(Total score: Mean±S.D.)		0± 0	0± 0
Landing foot splay (mm: Mean±S.D.)		65± 3	56±22

No significant difference between treated group and control group.

Table 2-75 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Grip strength of male rats (Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1589	804
	S.D.	185	160
40	No.	5	5
	Mean	1557	713
	S.D.	101	77
200	No.	5	5
	Mean	1486	719
	S.D.	137	99
1000	No.	5	5
	Mean	1593	806
	S.D.	126	116

No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-76 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Grip strength of female rats (Main group, Lactation day 4)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1147	669
	S.D.	219	155
40	No.	5	5
	Mean	1320	736
	S.D.	77	45
200	No.	5	5
	Mean	1371	696
	S.D.	155	120
1000	No.	5	5
	Mean	1352	699
	S.D.	163	40

No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-77 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Grip strength of female rats (Satellite group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1218	604
	S.D.	77	68
1000	No.	5	5
	Mean	1149	595
	S.D.	65	33

No.: No. of animals
No significant difference between treated group and control group.

Table 2-78 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Grip strength of male rats (Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1691	890
	S.D.	183	116
1000	No.	5	5
	Mean	1788	883
	S.D.	123	122

No.: No. of animals
No significant difference between treated group and control group.

Table 2-79 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Grip strength of female rats (Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1375	749
	S.D.	23	78
1000	No.	5	5
	Mean	1343	726
	S.D.	70	107

No.: No. of animals
No significant difference between treated group and control group.

Table 2-80 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Motor activity of male rats (Week 6 of administration)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	408	301	219	69	129	116	1242
	S.D.	27	115	117	103	80	125	221
40	No.	5	5	5	5	5	5	5
	Mean	368	307	183	87	91	57	1094
	S.D.	30	47	123	149	162	55	505
200	No.	5	5	5	5	5	5	5
	Mean	375	295	129	65	81	160	1106
	S.D.	59	65	63	69	115	147	331
1000	No.	5	5	5	5	5	5	5
	Mean	342	264	122	73	50	63	914
	S.D.	86	126	125	75	24	112	448

Unit: Count
No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-81 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Motor activity of female rats (Main group, Lactation day 4)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	310	167	133	32	43	45	730
	S.D.	113	81	124	49	68	38	362
40	No.	5	5	5	5	5	5	5
	Mean	281	185	143	183	114	86	991
	S.D.	110	166	151	146	97	91	625
200	No.	5	5	5	5	5	5	5
	Mean	254	140	84	76	72	93	719
	S.D.	55	57	73	69	106	99	328
1000	No.	5	5	5	5	5	5	5
	Mean	340	168	106	121	74	65	874
	S.D.	85	145	109	105	92	104	585

Unit: Count
No.: No. of animals
No significant difference in any treated groups from control group.

Table 2-82 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Motor activity of female rats (Satellite group, Week 6 of administration)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	415	366	106	43	66	58	1055
	S.D.	24	90	79	50	99	110	248
1000	No.	5	5	5	5	5	5	5
	Mean	368	229	134	137	203	137	1208
	S.D.	56	156	146	121	114	184	327

Unit: Count
No.: No. of animals
No significant difference between treated group and control group.

Table 2-83 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Motor activity of male rats (Week 2 of recovery)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	358	284	245	196	121	132	1337
	S.D.	44	111	146	66	66	166	444
1000	No.	5	5	5	5	5	5	5
	Mean	406	300	262	243	202	191	1604
	S.D.	25	6	102	102	165	124	491

Unit: Count
No.: No. of animals
No significant difference between treated group and control group.

Table 2-84 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Motor activity of female rats (Week 2 of recovery)

Dose mg/kg		Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
0	No.	5	5	5	5	5	5	5
	Mean	359	330	217	77	47	77	1107
	S.D.	7	20	118	86	62	140	204
1000	No.	5	5	5	5	5	5	5
	Mean	330	231	210	121	65	110	1068
	S.D.	62	145	128	120	132	109	508

Unit: Count
No.: No. of animals
No significant difference between treated group and control group.

Table 3-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of male rats (Administration period)

Dose mg/kg		Day of administration 1	8	15	22	29	36	42	Gain 1-42
0	No.	12	12	12	12	12	12	12	12
	Mean	415	435	457	471	491	510	519	104
	S.D.	22	25	29	29	25	25	26	14
40	No.	12	12	12	12	12	12	12	12
	Mean	414	431	448	465	487	508	516	102
	S.D.	20	25	31	34	39	43	43	26
200	No.	12	12	12	12	12	12	12	12
	Mean	415	429	445	462	478	496	503	88
	S.D.	22	24	27	29	30	31	35	22
1000	No.	12	12	12	12	12	12	12	12
	Mean	415	426	445	458	479	494	506	91
	S.D.	20	16	23	27	31	36	37	22

Unit: g
No.: No. of animals
No significant difference in any treated groups from control group.

Table 3-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg		Day of administration 1	8	15	Gain 1-15
0	No.	12	12	12	12
	Mean	253	262	272	19
	S.D.	16	18	18	6
40	No.	12	12	12	12
	Mean	251	261	269	19
	S.D.	16	17	17	7
200	No.	12	12	12	12
	Mean	257	263	273	16
	S.D.	16	16	17	6
1000	No.	12	12	12	12
	Mean	250	260	273	23
	S.D.	13	13	11	8

Unit: g
No.: No. of animals
No significant difference in any treated groups from control group.

Table 3-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of dams during the gestation period (Main group)

Dose mg/kg		Administration 0	7	14	20a)	Gain 0-20
0	No.	12	12	12	12	12
	Mean	278	313	347	420	142
	S.D.	20	20	18	35	29
40	No.	9	9	9	9	9
	Mean	281	319	354	438	157
	S.D.	20	19	18	20	20
200	No.	11	11	11	11	11
	Mean	277	320	356	441	164*
	S.D.	16	17	16	22	16D
1000	No.	12	12	12	12	12
	Mean	278	315	354	444	166*
	S.D.	9	12	14	16	10D

Unit: g
No.: No. of dams
a): Gestation day
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 3-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of dams during the lactation period (Main group)

Dose mg/kg		Administration 0	Administration 4a)	Gain 0-4
0	No.	11b)	11	11
	Mean	337	354	17
	S.D.	26	16	19
40	No.	9	9	9
	Mean	339	354	15
	S.D.	28	19	25
200	No.	11	11	11
	Mean	341	364	23
	S.D.	23	20	23
1000	No.	12	12	12
	Mean	338	362	24
	S.D.	19	16	21

Unit: g
No.: No. of dams
a): Lactation day
b): One dam was necropsied on lactation day 0 because all pups were stillborn.
No significant difference in any treated groups from control group.

Table 3-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of female rats (Satellite group, Administration period)

Dose mg/kg		Day of administration 1	8	15	22	29	36	42	Gain 1-42
0	No.	10	10	10	10	10	10	10	10
	Mean	251	264	272	279	287	297	299	49
	S.D.	14	9	14	17	13	14	17	12
1000	No.	10	10	10	10	10	10	10	10
	Mean	255	266	276	284	293	301	305	50
	S.D.	17	17	23	21	19	21	21	9

Unit: g
No.: No. of animals
No significant difference between treated group and control group.

Table 3-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of male rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14	Gain 1-14
0	No.	5	5	5	5
	Mean	507	521	528	21
	S.D.	32	34	33	2
1000	No.	5	5	5	5
	Mean	504	522	534	30
	S.D.	56	62	63	10

Unit: g
No.: No. of animals
No significant difference between treated group and control group.

Table 3-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of female rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14	Gain 1-14
0	No.	5	5	5	5
	Mean	297	308	308	11
	S.D.	18	15	13	6
1000	No.	5	5	5	5
	Mean	306	308	308	2*
	S.D.	22	24	21	5T

Unit: g
No.: No. of animals
*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 4-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of male rats (Administration period)

Dose mg/kg		Day of administration 2	8	15	30	36	42
0	No.	12	12	12	12	12	12
	Mean	29	28	29	28	28	29
	S.D.	3	3	3	2	3	2
40	No.	12	12	12	12	12	12
	Mean	28	27	28	28	30	30
	S.D.	3	3	3	3	2	3
200	No.	12	12	12	12	12	12
	Mean	28	26	27	28	29	29
	S.D.	3	2	2	2	3	4
1000	No.	12	12	12	12	12	12
	Mean	27	24	29	28	28	30
	S.D.	3	8	2	3	3	3

Unit: g/rat/day
No.: No. of animals
No significant difference in any treated groups from control group.

Table 4-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of female rats during the pre-mating period (Main group)

Dose mg/kg		Day of administration 2	8	15
0	No.	12	12	12
	Mean	20	21	21
	S.D.	3	4	4
40	No.	12	12	12
	Mean	21	20	21
	S.D.	3	3	3
200	No.	12	12	12
	Mean	22	18	22
	S.D.	3	3	3
1000	No.	12	12	12
	Mean	22	21	22
	S.D.	3	3	2

Unit: g/rat/day
No.: No. of animals
No significant difference in any treated groups from control group.

Table 4-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of dams during the gestation period (Main group)

Dose mg/kg		Administration 1	7	14	20a)
0	No.	12	12	12	12
	Mean	24	27	26	25
	S.D.	3	3	3	3
40	No.	9	9	9	9
	Mean	23	28	29	25
	S.D.	4	4	3	2
200	No.	11	11	11	11
	Mean	24	28	27	25
	S.D.	2	3	3	3
1000	No.	12	12	12	12
	Mean	24	27	27	26
	S.D.	3	3	3	3

Unit: g/rat/day
No.: No. of dams
a): Gestation day
No significant difference in any treated groups from control group.

Table 4-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of dams during the lactation period (Main group)

Dose mg/kg		Administration 2	4a)
0	No.	11b)	11
	Mean	38	45
	S.D.	25	6
40	No.	9	9
	Mean	27	47
	S.D.	9	5
200	No.	11	11
	Mean	31	48
	S.D.	7	5
1000	No.	12	12
	Mean	37	50*
	S.D.	5	5D

Unit: g/rat/day
No.: No. of dams
a): Lactation day
b): One dam was necropsied on lactation day 0 because all pups were stillborn.
*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 4-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of female rats (Satellite group, Administration period)

Dose mg/kg		Day of administration 2	8	15	30	36	42
0	No.	10	10	10	10	10	10
	Mean	20	21	20	20	21	22
	S.D.	2	3	2	4	3	3
1000	No.	10	10	10	10	10	10
	Mean	18	20	21	21	20	22
	S.D.	2	2	3	4	3	3

Unit: g/rat/day
No.: No. of animals
No significant difference between treated group and control group.

Table 4-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of male rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14
0	No.	5	5	5
	Mean	28	30	28
	S.D.	2	4	2
1000	No.	5	5	5
	Mean	30	30	30
	S.D.	4	4	5

Unit: g/rat/day
No.: No. of animals
No significant difference between treated group and control group.

Table 4-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Food consumption of female rats (Recovery period)

Dose mg/kg		Day of recovery 1	8	14
0	No.	5	5	5
	Mean	19	24	21
	S.D.	3	1	4
1000	No.	5	5	5
	Mean	21	21	22
	S.D.	1	5	3

Unit: g/rat/day
No.: No. of animals
No significant difference between treated group and control group.

Table 5-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	0	1	0	2	2	0	2	3	0	0	0	4	1	0	0	5	0	0	0	0
40	5	0	0	0	0	0	0	1	3	1	0	1	4	0	0	0	2	3	0	0	5	0	0	0	0
200	5	0	0	0	0	1	0	0	1	3	0	2	2	1	0	0	3	2	0	0	5	0	0	0	0
1000	5	0	0	0	0	0	1	4	0	0	0	1	2	2	0	0	1	4	0	0	4	1	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				T-BIL(mg/dL)	Urobilinogen 6)				Color 7)				
		-	+-	+	++	+++	-	+	++	+++	0.0	+-	+	++	+++	LY	Y	DY	LP	B
0	5	3	2	0	0	0	5	0	0	0	5	5	0	0	0	0	5	0	0	0
40	5	5	0	0	0	0	5	0	0	0	5	5	0	0	0	0	5	0	0	0
200	5	4	0	0	0	1	5	0	0	0	5	5	0	0	0	0	5	0	0	0
1000	5	4	1	0	0	0	0	3	1	1	5	5	0	0	0	0	0	0	5	0

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown

Table 5-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
40	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	4	0	0	0	5	0	0	0	0
200	5	4	1	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	2	3	0	0	0	5	0	0	0	0
1000	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Water intake and urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	40	16.8	2153	1.90	5.63	2.50
		S.D.	5	5.3	322	0.54	1.63	0.73
40	5	Mean	50	24.3	1736	2.46	6.25	2.87
		S.D.	11	7.5	297	0.56	1.11	0.68
200	5	Mean	36	16.3	1865	2.59	4.28	2.18
		S.D.	11	2.9	187	0.37	1.01	0.22
1000	5	Mean	47	16.3	2343	5.55**	4.60	2.82
		S.D.	12	2.8	340	0.46D	0.47	0.19

**: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 5-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	0	1	1	1	2	4	1	0	0	0	5	0	0	0	0	5	0	0	0	0
1000	5	0	0	0	0	1	2	0	2	0	0	1	1	3	0	3	2	0	0	0	3	2	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.	Occult blood 4) -	+-	+	++	+++	Bilirubin 5) -	+	++	+++	T-BIL(mg/dL) 0.0	Urobilinogen 6) +-	+	++	+++	Color 7) LY	Y	DY	LP	B
0	5	5	0	0	0	0	5	0	0	0	5	5	0	0	0	0	5	0	0	0
1000	5	2	2	0	1	0	1	2	1	1	5	3	2	0	0	0	0	0	5	0

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown

Table 5-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																
																									CRYSTALLIZATION									
		RBC					WBC					SEC					SREC					Cast			PS					CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	2	3	0	0	0	5	0	0	0	0
1000	5	4	0	0	1	0	4	0	0	1	0	0	5	0	0	0	5	0	0	0	0	5	0	0	2	3	0	0	0	5	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

- : Negative
+- : Slight
+ : Mild
++ : Moderate
+++ : Severe

Table 5-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Water intake and urinalysis of female rats (Satellite group, Week 6 of administration)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	30	9.7	2368	1.20	3.30	1.47
		S.D.	5	3.5	500	0.20	0.75	0.36
1000	5	Mean	39	13.8	2066	3.16**	2.77	1.68
		S.D.	17	7.2	874	0.37T	0.38	0.23

**: p<0.01 (Significant difference from control group)
T: Student's t-test

Table 5-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	0	0	1	2	2	0	2	3	0	0	0	4	1	0	0	5	0	0	0	0
1000	5	0	0	0	0	0	0	0	3	2	0	1	3	1	0	0	4	1	0	0	5	0	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				T-BIL(mg/dL)	Urobilinogen 6)				Color 7)				
		-	+-	+	++	+++	-	+	++	+++	0.0	+-	+	++	+++	LY	Y	DY	LP	B
0	5	4	0	0	0	1	5	0	0	0	5	5	0	0	0	0	5	0	0	0
1000	5	3	2	0	0	0	1	3	1	0	5	5	0	0	0	0	4	0	0	1

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown

Table 5-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	4	0	0	0	5	0	0	0	0
1000	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Water intake and urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	45	18.5	1935	1.64	5.50	2.37
		S.D.	13	8.5	219	0.56	1.83	0.74
1000	5	Mean	39	17.3	2161	1.65	5.94	2.51
		S.D.	8	3.8	319	0.26	0.70	0.39

No significant difference between treated group and control group.

Table 5-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	pH									Protein 1)					Ketone body 2)					Glucose 3)				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	>=9.0	-	+-	+	++	+++	-	+-	+	++	+++	-	+	++	+++	++++
0	5	0	0	0	0	1	2	0	1	1	3	1	1	0	0	5	0	0	0	0	5	0	0	0	0
1000	5	0	0	0	0	2	0	1	1	1	2	1	0	2	0	4	1	0	0	0	5	0	0	0	0

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL

Table 5-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	Occult blood 4)					Bilirubin 5)				T-BIL(mg/dL)	Urobilinogen 6)				Color 7)				
		-	+-	+	++	+++	-	+	++	+++	0.0	+-	+	++	+++	LY	Y	DY	LP	B
0	5	5	0	0	0	0	4	1	0	0	5	5	0	0	0	0	5	0	0	0
1000	5	3	2	0	0	0	3	1	1	0	5	5	0	0	0	0	5	0	0	0

4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown

Table 5-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	5	5	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	0	0
1000	5	4	0	0	0	1	4	0	1	0	0	0	5	0	0	0	5	0	0	0	0	5	0	0	1	4	0	0	0	5	0	0	0	0

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Table 5-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Water intake and urinalysis of female rats (Week 2 of recovery)

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
0	5	Mean	33	10.2	2310	1.14	3.66	1.49
		S.D.	5	1.5	191	0.18	0.50	0.09
1000	5	Mean	35	12.9	2213	1.22	3.85	1.58
		S.D.	8	6.2	742	0.29	0.86	0.42

No significant difference between treated group and control group.

Table 6-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	920	16.1	46.1	50.1	17.5	34.8	2.0	111.9	13.9	18.9	254
		S.D.	15	0.4	1.2	1.3	0.5	0.2	0.2	7.4	1.5	1.1	31
40	5	Mean	899	16.0	45.5	50.7	17.8	35.1	2.0	97.6	13.3	17.7	251
		S.D.	40	0.4	1.3	1.2	0.5	0.5	0.4	2.5	1.3	1.4	19
200	5	Mean	901	15.6	44.8	49.8	17.3	34.8	2.3	112.7	15.1	18.0	265
		S.D.	37	0.4	1.4	1.6	0.4	0.4	0.3	9.5	0.8	0.8	13
1000	5	Mean	898	15.6	44.6	49.7	17.4	35.0	2.4	108.6	18.6**	19.5	250
		S.D.	25	0.7	1.8	2.4	1.0	0.6	0.5	13.6	2.2D	1.1	19

**: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 6-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of male rats (End of administration)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	74.2	75.5	19.7	1.2	0.4	2.9	0.3	56.5	14.1	0.9	0.3	2.1	0.3
		S.D.	22.9	4.0	4.0	0.3	0.1	1.2	0.1	19.9	2.9	0.3	0.1	1.0	0.2
40	5	Mean	79.4	75.8	19.9	1.2	0.4	2.5	0.3	60.1	15.8	0.9	0.3	1.9	0.2
		S.D.	10.6	3.9	3.9	0.2	0.1	0.6	0.1	8.2	4.1	0.3	0.1	0.4	0.1
200	5	Mean	75.4	75.5	19.9	1.3	0.5	2.5	0.4	57.1	14.8	1.0	0.4	2.0	0.3
		S.D.	12.4	3.0	3.5	0.2	0.2	0.7	0.1	10.9	2.3	0.3	0.2	0.8	0.1
1000	5	Mean	95.1	72.1	23.3	1.1	0.4	2.7	0.3	67.2	23.5	1.1	0.4	2.7	0.3
		S.D.	29.7	7.3	6.9	0.3	0.2	0.6	0.0	17.5	12.0	0.5	0.1	1.3	0.1

LUC: Large unstained cells
No significant difference in any treated groups from control group.

Table 6-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	714	13.5	39.3	55.3	19.0	34.4	6.7	131.0	11.7	15.4	263
		S.D.	67	1.0	2.5	2.5	0.6	0.6	1.6	13.1	0.6	3.0	34
40	5	Mean	715	13.6	39.4	55.0	18.9	34.4	6.7	140.8	11.5	13.0	258
		S.D.	42	0.7	2.3	1.7	0.7	0.4	2.2	26.2	0.7	0.7	27
200	5	Mean	694	13.4	38.7	55.8	19.4	34.7	7.8	137.9	12.1	14.3	278
		S.D.	37	0.7	1.6	1.3	0.5	0.5	0.8	13.5	0.8	0.4	70
1000	5	Mean	704	13.9	39.7	56.4	19.8	35.0	7.6	133.0	11.8	14.7	260
		S.D.	30	0.1	0.5	1.9	0.7	0.2	1.1	11.4	1.1	1.1	42

No significant difference in any treated groups from control group.

Table 6-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (Lactation day 5)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	115.8	61.8	33.8	0.9	0.2	2.9	0.5	70.8	39.9	1.0	0.2	3.4	0.5
		S.D.	13.9	7.4	6.9	0.5	0.1	0.5	0.2	3.8	13.4	0.5	0.1	0.9	0.2
40	5	Mean	113.5	58.7	35.9	1.0	0.3	3.8	0.4	66.1	41.2	1.1	0.3	4.3	0.4
		S.D.	14.4	10.4	11.5	0.9	0.1	0.8	0.2	11.3	16.6	1.0	0.1	1.1	0.2
200	5	Mean	107.8	56.8	38.5	1.2	0.2	2.9	0.4	61.0	41.8	1.2	0.3	3.0	0.4
		S.D.	16.4	7.4	7.9	0.5	0.1	0.9	0.1	10.8	11.5	0.4	0.1	0.7	0.2
1000	5	Mean	129.2	55.6	39.6	1.0	0.3	3.1	0.3	72.3	50.7	1.3	0.4	4.0	0.5
		S.D.	32.7	3.0	3.3	0.3	0.1	1.3	0.1	20.3	11.3	0.4	0.2	1.9	0.1

LUC: Large unstained cells
No significant difference in any treated groups from control group.

Table 6-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (Satellite group, End of administration)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	807	15.2	42.8	53.0	18.8	35.4	2.4	110.2	11.7	15.3	189
		S.D.	10	0.2	1.0	1.5	0.4	0.4	0.4	10.1	0.3	2.3	12
1000	5	Mean	787	14.9	41.6	52.8	19.0	35.9	2.4	112.2	11.6	15.9	158*
		S.D.	20	0.4	0.8	0.5	0.2	0.5	0.2	9.3	0.8	2.0	19T

*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 6-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (Satellite group, End of administration)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	53.4	79.5	14.9	1.8	0.4	2.8	0.5	42.8	7.7	0.9	0.2	1.5	0.3
		S.D.	13.9	4.9	4.1	0.8	0.1	0.9	0.3	12.9	1.7	0.3	0.1	0.7	0.2
1000	5	Mean	77.6	80.0	15.9	1.3	0.4	1.9	0.6	62.0	12.3	1.0	0.3	1.5	0.5
		S.D.	22.4	4.6	4.2	0.2	0.1	0.5	0.3	18.2	5.0	0.3	0.1	0.7	0.3

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 6-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	926	16.9	47.2	51.0	18.2	35.8	1.7	94.9	15.6	19.8	261
		S.D.	19	0.4	1.0	1.8	0.7	0.4	0.4	3.4	1.8	2.2	26
1000	5	Mean	920	16.5	46.3	50.4	17.9	35.6	1.9	99.7	15.8	19.2	259
		S.D.	36	0.5	1.6	1.5	0.3	0.7	0.3	10.4	2.0	1.0	44

No significant difference between treated group and control group.

Table 6-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of male rats (End of recovery)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	78.7	80.4	14.2	1.8	0.4	2.5	0.6	63.2	11.3	1.4	0.3	2.0	0.4
		S.D.	13.5	1.5	1.7	0.5	0.1	1.1	0.5	10.0	3.2	0.2	0.1	1.0	0.4
1000	5	Mean	87.1	78.5	16.2	1.5	0.4	2.6	0.8	69.0	13.6	1.3	0.4	2.1	0.7
		S.D.	28.4	3.1	2.6	0.5	0.2	0.5	0.4	24.6	2.6	0.7	0.2	0.4	0.5

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 6-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (End of recovery)

Dose mg/kg	No.		RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
0	5	Mean	815	15.3	42.7	52.3	18.8	36.0	1.9	116.2	12.0	14.4	187
		S.D.	22	0.4	0.9	1.3	0.3	0.4	0.2	10.8	0.5	1.3	23
1000	5	Mean	810	15.2	42.3	52.2	18.7	35.9	2.2	109.6	12.2	15.9	184
		S.D.	33	0.3	1.0	0.9	0.4	0.3	0.4	11.8	0.5	2.0	21

No significant difference between treated group and control group.

Table 6-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Hematology of female rats (End of recovery)

Dose mg/kg	No.		WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
			10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	61.1	79.7	15.9	1.3	0.3	2.3	0.5	49.6	8.9	0.8	0.2	1.3	0.4
		S.D.	18.8	8.6	8.4	0.3	0.1	0.4	0.2	19.3	3.3	0.2	0.1	0.3	0.3
1000	5	Mean	65.4	77.6	17.4	1.4	0.3	2.7	0.5	50.5	11.7	0.9	0.2	1.8	0.3
		S.D.	23.9	9.9	9.5	0.3	0.1	0.7	0.2	19.7	7.6	0.3	0.1	0.7	0.2

LUC: Large unstained cells
No significant difference between treated group and control group.

Table 7-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of male rats (End of administration)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	67	32	42	0	415	10.0	47	24	74	0.1	127
		S.D.	7	3	7	1	69	5.3	5	16	10	0.1	21
40	5	Mean	74	35	45	0	344	8.8	44	33	73	0.1	118
		S.D.	10	10	12	1	41	3.5	8	20	12	0.1	11
200	5	Mean	68	28	39	0	396	10.3	47	26	75	0.1	122
		S.D.	7	3	5	0	54	5.6	8	8	9	0.1	14
1000	5	Mean	69	33	41	0	333	24.6*	48	40	83	0.0	118
		S.D.	8	9	12	0	53	12.0D	8	13	8	0.0	10

*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 7-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of male rats (End of administration)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	15	0.28	143	4.6	107	9.6	5.8	5.8	3.3	1.32
		S.D.	3	0.03	1	0.1	2	0.2	0.3	0.2	0.2	0.12
40	5	Mean	14	0.26	144	4.7	107	9.5	5.5	5.7	3.2	1.27
		S.D.	1	0.04	1	0.2	2	0.2	0.3	0.2	0.2	0.09
200	5	Mean	15	0.26	142	4.6	106	9.5	6.1	5.7	3.2	1.28
		S.D.	2	0.03	2	0.1	2	0.3	0.6	0.3	0.2	0.13
1000	5	Mean	15	0.24	142	4.1*	102**	9.5	5.6	5.5	3.2	1.42
		S.D.	2	0.02	2	0.4D	3D	0.3	0.3	0.2	0.1	0.17

*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
D: Dunnett's test

Table 7-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (Lactation day 5)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	94	54	50	1	265	20.9	57	63	114	0.1	119
		S.D.	28	12	8	0	105	22.5	10	24	19	0.0	12
40	5	Mean	89	53	42	0	257	12.8	54	39	107	0.1	124
		S.D.	16	12	5	0	86	3.6	16	13	30	0.0	8
200	5	Mean	87	52	49	1	216	17.9	58	49	118	0.1	128
		S.D.	15	10	12	1	60	6.9	18	15	29	0.0	7
1000	5	Mean	101	55	46	1	329	22.6	55	57	115	0.1	116
		S.D.	13	11	10	0	83	7.9	10	15	18	0.1	14

No significant difference in any treated groups from control group.

Table 7-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (Lactation day 5)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	14	0.27	140	4.0	106	10.1	6.1	5.9	3.5	1.48
		S.D.	2	0.02	1	0.3	2	0.2	1.0	0.2	0.2	0.19
40	5	Mean	17	0.30	140	4.2	106	10.0	6.4	6.0	3.5	1.42
		S.D.	2	0.06	1	0.2	2	0.2	0.2	0.5	0.3	0.11
200	5	Mean	15	0.26	140	4.4	106	10.1	6.9	6.2	3.7	1.51
		S.D.	1	0.02	1	0.3	2	0.4	0.7	0.3	0.1	0.08
1000	5	Mean	17*	0.25	139	4.2	104	10.2	7.4	6.1	3.6	1.46
		S.D.	3D	0.03	2	0.2	2	0.3	1.3	0.2	0.1	0.03

*: $p<0.05$ (Significant difference from control group)
D: Dunnett's test

Table 7-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (Satellite group, End of administration)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	125	69	70	1	175	19.8	67	18	124	0.1	126
		S.D.	134	91	62	0	33	10.8	14	5	21	0.0	10
1000	5	Mean	56	20	39	1	186	17.0	62	24	123	0.0**	135
		S.D.	8	4	2	1	77	9.0	3	6	8	0.0T	11

**: p<0.01 (Significant difference from control group)
T: Student's t-test

Table 7-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (Satellite group, End of administration)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	17	0.33	142	4.5	108	9.8	3.9	6.2	3.8	1.58
		S.D.	1	0.02	1	0.3	1	0.3	0.4	0.3	0.2	0.16
1000	5	Mean	18	0.33	140	4.0	105**	9.6	4.1	5.9	3.7	1.63
		S.D.	1	0.04	2	0.5	2AT	0.2	0.2	0.3	0.2	0.13

**: p<0.01 (Significant difference from control group)
AT: Aspin-Welch t-test

Table 7-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of male rats (End of recovery)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	63	30	45	0	328	7.5	42	44	73	0.1	113
		S.D.	5	3	8	0	41	1.2	6	21	6	0.0	6
1000	5	Mean	62	28	42	1	282	13.6*	49	34	77	0.1	120
		S.D.	7	4	4	1	29	4.8AT	10	11	12	0.0	10

*: $p<0.05$ (Significant difference from control group)
AT: Aspin-Welch t-test

Table 7-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of male rats (End of recovery)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	15	0.28	142	4.5	105	9.6	5.9	5.9	3.3	1.26
		S.D.	2	0.02	1	0.2	1	0.1	0.2	0.2	0.1	0.08
1000	5	Mean	16	0.25	142	4.6	106	9.5	5.9	5.8	3.2	1.26
		S.D.	1	0.01	0	0.2	2	0.3	0.5	0.3	0.1	0.14

No significant difference between treated group and control group.

Table 7-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (End of recovery)

Dose mg/kg	No.		AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
0	5	Mean	65	34	38	1	191	13.4	68	19	122	0.1	127
		S.D.	7	5	4	1	79	5.9	15	4	20	0.0	22
1000	5	Mean	58	28	37	1	125	10.4	68	31	127	0.1	131
		S.D.	5	6	4	1	11	2.2	12	16	20	0.0	13

No significant difference between treated group and control group.

Table 7-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Blood chemistry of female rats (End of recovery)

Dose mg/kg	No.		BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
0	5	Mean	18	0.32	141	4.4	108	10.0	4.1	6.2	3.7	1.50
		S.D.	3	0.03	1	0.1	1	0.3	0.5	0.2	0.2	0.14
1000	5	Mean	19	0.32	140*	4.4	106**	9.8	3.5	6.2	3.7	1.47
		S.D.	3	0.02	1T	0.2	1T	0.3	0.6	0.2	0.1	0.14

*: $p<0.05$; **: $p<0.01$ (Significant difference from control group)
T: Student's t-test

Table 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of male rats (End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	7	7	7	7	7	7	7
		Mean	501	2.13	13.6	24.1	309	1.44	12.37
		S.D.	15	0.08	1.2	3.4	86	0.10	0.49
	40	No.	12	12	12	12	12	12	12
		Mean	486	2.12	13.5	25.0	274	1.47	11.97
		S.D.	42	0.07	1.3	5.3	68	0.14	1.83
	200	No.	12	12	12	12	12	12	12
		Mean	473	2.11	14.0	22.5	277	1.41	11.60
		S.D.	33	0.08	1.8	3.8	74	0.17	1.32
	1000	No.	7	7	7	7	7	7	7
		Mean	477	2.15	13.4	23.9	312	1.44	12.79
		S.D.	22	0.08	1.5	2.6	109	0.13	1.27
Relative	0	No.		7	7	7	7	7	7
		Mean		0.43	2.7	4.8	62	0.29	2.47
		S.D.		0.02	0.2	0.7	18	0.02	0.09
	40	No.		12	12	12	12	12	12
		Mean		0.44	2.8	5.2	57	0.30	2.45
		S.D.		0.04	0.2	1.2	16	0.02	0.18
	200	No.		12	12	12	12	12	12
		Mean		0.45	3.0	4.8	59	0.30	2.45
		S.D.		0.03	0.3	0.8	15	0.02	0.16
	1000	No.		7	7	7	7	7	7
		Mean		0.45	2.8	5.0	65	0.30	2.68
		S.D.		0.03	0.3	0.6	21	0.02	0.21

No significant difference in any treated groups from control group.

Table 8-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of male rats (End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
		No.	7	7	7	7	7	7	7
Absolute	0	Mean	0.72	3.36	63	3.39	1330	1.72	1.29
		S.D.	0.10	0.11	7	0.23	74	0.28	0.16
		No.	12	12	12	12	12	12	12
	40	Mean	0.76	3.53	63	3.35	1292	1.70	1.28
		S.D.	0.12	0.34	10	0.25	108	0.37	0.19
		No.	12	12	12	12	12	12	12
	200	Mean	0.75	3.47	62	3.32	1319	1.86	1.38
		S.D.	0.10	0.29	8	0.19	75	0.25	0.34
		No.	7	7	7	7	7	7	7
	1000	Mean	0.77	3.72	59	3.28	1310	1.82	1.32
		S.D.	0.09	0.28	8	0.30	79	0.15	0.17
		No.	7	7	7	7	7	7	7
Relative	0	Mean	0.14	0.67	13	0.68	265	0.34	0.26
		S.D.	0.02	0.03	2	0.04	13	0.06	0.03
		No.	12	12	12	12	12	12	12
	40	Mean	0.16	0.73	13	0.69	267	0.35	0.27
		S.D.	0.02	0.06	1	0.05	27	0.09	0.04
		No.	12	12	12	12	12	12	12
	200	Mean	0.16	0.73*	13	0.70	280	0.39	0.29
		S.D.	0.01	0.05D	2	0.04	23	0.05	0.07
		No.	7	7	7	7	7	7	7
	1000	Mean	0.16	0.78**	12	0.69	275	0.38	0.28
		S.D.	0.02	0.06D	2	0.07	21	0.02	0.04

*: p<0.05; **: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 8-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (Main group, End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	11	11	11	11	11	11	11
		Mean	318	2.00	19.1	18.9	227	1.07	10.65
		S.D.	18	0.08	2.9	2.7	57	0.11	0.61
	40	No.	9	9	9	9	9	9	9
		Mean	320	2.00	19.6	17.7	183	1.08	10.75
		S.D.	19	0.07	3.0	2.8	53	0.07	1.05
	200	No.	11	11	11	11	11	11	11
		Mean	320	2.03	20.0	19.6	225	1.06	10.92
		S.D.	18	0.05	2.7	3.6	65	0.10	0.96
	1000	No.	12	12	12	12	12	12	12
		Mean	328	2.02	19.4	17.6	235	1.12	11.33
		S.D.	16	0.05	2.3	3.3	44	0.09	0.48
Relative	0	No.		11	11	11	11	11	11
		Mean		0.63	6.0	6.0	71	0.34	3.36
		S.D.		0.04	1.0	1.0	19	0.04	0.15
	40	No.		9	9	9	9	9	9
		Mean		0.63	6.1	5.5	57	0.34	3.36
		S.D.		0.03	0.9	0.9	17	0.02	0.25
	200	No.		11	11	11	11	11	11
		Mean		0.64	6.3	6.1	70	0.33	3.41
		S.D.		0.04	0.7	1.1	18	0.03	0.25
	1000	No.		12	12	12	12	12	12
		Mean		0.62	5.9	5.4	72	0.34	3.46
		S.D.		0.03	0.6	1.0	13	0.03	0.19

No significant difference in any treated groups from control group.

Table 8-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (Main group, End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	11	11	11	11	11
		Mean	0.68	2.25	84	109.4	664
		S.D.	0.07	0.18	9	20.6	122
	40	No.	9	9	9	9	9
		Mean	0.67	2.17	83	108.8	671
		S.D.	0.10	0.29	12	12.4	107
	200	No.	11	11	11	11	11
		Mean	0.70	2.30	82	101.8	707
		S.D.	0.14	0.26	12	16.9	111
	1000	No.	12	12	12	12	12
		Mean	0.78	2.49*	83	103.3	697
		S.D.	0.09	0.18D	7	7.3	95
Relative	0	No.	11	11	11	11	11
		Mean	0.21	0.71	26	34.5	209
		S.D.	0.02	0.05	3	6.0	35
	40	No.	9	9	9	9	9
		Mean	0.21	0.68	26	34.0	209
		S.D.	0.02	0.07	3	2.7	25
	200	No.	11	11	11	11	11
		Mean	0.22	0.72	26	31.7	221
		S.D.	0.04	0.06	4	4.5	35
	1000	No.	12	12	12	12	12
		Mean	0.24	0.76	26	31.5	213
		S.D.	0.03	0.04	2	2.4	27

*: p<0.05 (Significant difference from control group)
D: Dunnett's test

Table 8-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (Satellite group, End of administration)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	280	1.95	18.9	17.5	288	0.90	7.19
		S.D.	19	0.09	0.8	2.9	56	0.07	0.50
	1000	No.	5	5	5	5	5	5	5
		Mean	285	2.00	18.4	19.2	366	0.92	7.78
		S.D.	17	0.04	2.0	3.3	110	0.04	0.40
Relative	0	No.		5	5	5	5	5	5
		Mean		0.70	6.8	6.3	102	0.32	2.57
		S.D.		0.05	0.5	1.1	15	0.03	0.10
	1000	No.		5	5	5	5	5	5
		Mean		0.70	6.5	6.8	127	0.32	2.73*
		S.D.		0.05	0.7	1.2	31	0.02	0.10T

*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 8-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (Satellite group, End of administration)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	5	5	5	5	5
		Mean	0.54	1.91	67	87.3	606
		S.D.	0.05	0.08	7	5.7	191
	1000	No.	5	5	5	5	5
		Mean	0.56	2.15*	70	97.6	706
		S.D.	0.08	0.20AT	6	9.0	102
Relative	0	No.	5	5	5	5	5
		Mean	0.19	0.68	24	31.4	215
		S.D.	0.01	0.05	3	3.9	60
	1000	No.	5	5	5	5	5
		Mean	0.20	0.76	24	34.2	246
		S.D.	0.02	0.07	2	2.2	26

*: $p<0.05$ (Significant difference from control group)
AT: Aspin-Welch t-test

Table 8-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of male rats (End of recovery)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	494	2.12	13.3	23.8	205	1.54	12.44
		S.D.	32	0.09	1.8	4.9	53	0.12	1.06
	1000	No.	5	5	5	5	5	5	5
		Mean	501	2.15	14.2	27.8	257	1.47	12.63
		S.D.	59	0.09	2.4	7.4	81	0.16	2.17
Relative	0	No.		5	5	5	5	5	5
		Mean		0.43	2.7	4.8	42	0.31	2.52
		S.D.		0.03	0.3	0.7	12	0.01	0.15
	1000	No.		5	5	5	5	5	5
		Mean		0.43	2.8	5.5	50	0.29*	2.51
		S.D.		0.03	0.2	0.9	12	0.01T	0.13

*: $p<0.05$ (Significant difference from control group)
T: Student's t-test

Table 8-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of male rats (End of recovery)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	0.70	3.43	61	3.05	1294	1.62	1.44
		S.D.	0.03	0.24	5	0.34	114	0.27	0.24
	1000	No.	5	5	5	5	5	5	5
		Mean	0.68	3.67	61	3.44	1420	1.72	1.22
		S.D.	0.13	0.55	9	0.35	164	0.20	0.18
Relative	0	No.	5	5	5	5	5	5	5
		Mean	0.14	0.69	12	0.62	262	0.33	0.29
		S.D.	0.01	0.02	2	0.05	23	0.05	0.05
	1000	No.	5	5	5	5	5	5	5
		Mean	0.13	0.73	12	0.69	284	0.35	0.24
		S.D.	0.01	0.05	1	0.06	20	0.04	0.03

No significant difference between treated group and control group.

Table 8-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (End of recovery)

	Dose mg/kg		Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)	Heart g(g/100g BW)	Liver g(g/100g BW)
Absolute	0	No.	5	5	5	5	5	5	5
		Mean	290	1.96	18.3	15.4	294	0.92	7.37
		S.D.	11	0.05	1.2	3.1	38	0.06	0.53
	1000	No.	5	5	5	5	5	5	5
		Mean	292	1.99	16.7	15.3	277	0.95	7.65
		S.D.	20	0.08	2.1	3.2	68	0.06	0.99
Relative	0	No.		5	5	5	5	5	5
		Mean		0.68	6.3	5.3	102	0.32	2.54
		S.D.		0.02	0.3	0.8	15	0.02	0.11
	1000	No.		5	5	5	5	5	5
		Mean		0.68	5.7	5.3	96	0.33	2.61
		S.D.		0.05	0.7	1.2	27	0.02	0.16

No significant difference between treated group and control group.

Table 8-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Organ weight of female rats (End of recovery)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	0	No.	5	5	5	5	5
		Mean	0.53	1.96	61	91.1	559
		S.D.	0.08	0.07	7	9.8	114
	1000	No.	5	5	5	5	5
		Mean	0.57	2.06	62	101.5	623
		S.D.	0.13	0.18	11	28.3	155
Relative	0	No.	5	5	5	5	5
		Mean	0.18	0.68	21	31.4	192
		S.D.	0.03	0.03	3	2.8	34
	1000	No.	5	5	5	5	5
		Mean	0.19	0.70	21	34.6	213
		S.D.	0.04	0.06	3	8.9	49

No significant difference between treated group and control group.

Table 9-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	7	12	12	7
General descriptions					
Discoloration,blue,subcutaneous,systemic		0	0	0	4
Kidney					
Discoloration,black,bilateral		0	0	0	5
Lung(bronchus)					
Focus,black		0	0	0	1
Stomach					
Focus,dark red,glandular stomach		1	0	0	0
Thickening,limiting ridge		0	0	0	1
Testis					
Discoloration,blue,bilateral		0	0	0	4

M : Male

Table 9-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	1000
Findings	Number:	5	5
General descriptions			
Discoloration,blue,subcutaneous,systemic		0	5
Kidney			
Discoloration,black,bilateral		0	5

F : Female

Table 9-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	11	9	11	12
General descriptions					
Discoloration,blue,subcutaneous,systemic		0	0	0	3
Kidney					
Discoloration,black,bilateral		0	0	0	5
Lung(bronchus)					
Focus,dark red		0	1	0	0
Stomach					
Focus,dark red,glandular stomach		1	1	0	2
Thickening,limiting ridge		0	0	0	1

F : Female

Table 9-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose(mg/kg):	0	1000
Findings	Number:	5	5
Testis			
Discoloration,blue,bilateral		0	3

M : Male

Table 9-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (End of recovery period)

Organs	Sex:	F	F
	Dose(mg/kg):	0	1000
Findings	Number:	5	5
Kidney			
Discoloration,black,bilateral		0	1
Liver			
Discoloration,black		0	1
Stomach			
Focus,dark red,glandular stomach		1	0
Urinary bladder			
Thickening,wall		0	1
Calculus		0	1
Tissue around the urethral orifice			
Swelling		0	1

F : Female

Table 9-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (Undelivered)

Organs	Sex:	F	F
	Dose(mg/kg):	40	200
Findings	Number:	3	1
All tissues			
Not remarkable		3	1

F : Female

Table 9-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Gross pathological findings (All littermates died)

Organs	Sex:	F
	Dose(mg/kg):	0
Findings	Number:	1
Uterus		
Prolapse		1
Thickening,wall,horn,unilateral		1

F : Female

Table 10-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	7	12	12	7
Adrenal					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Bone+Bone marrow,femoral					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Cerebellum(Pons)					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Cerebrum					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Epididymis					
Number examined		5	3	1	5
Not remarkable		5	3	1	4
Cell debris,lumen		0	0	0	1
minimal		0	0	0	1
Eye					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Heart					
Number examined		5	3	1	5
Not remarkable		4	3	1	3
Cell infiltration,interstitial		1	0	0	2
minimal		1	0	0	2
Intestine,duodenum					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Intestine,jejunum					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Intestine,ileum(Peyer's patch)					
Number examined		5	3	1	5
Not remarkable		5	3	1	4
Cell infiltration,mucosal		0	0	0	1
mild		0	0	0	1
Intestine,cecum					
Number examined		5	8	6	5
Not remarkable		5	8	6	1
Hyperplasia,mucosal,diffuse		0	0	0	4
minimal		0	0	0	4
Intestine,colon					
Number examined		5	8	6	5
Not remarkable		5	8	6	2
Hyperplasia,mucosal,diffuse		0	0	0	3
minimal		0	0	0	3
Intestine,rectum					
Number examined		5	8	6	5
Not remarkable		5	8	6	2
Hyperplasia,mucosal,diffuse		0	0	0	3
minimal		0	0	0	3

M : Male

Table 10-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs / Findings	Sex: / Dose(mg/kg): / Number:	M 0 7	M 40 12	M 200 12	M 1000 7
Kidney					
Number examined		5	8	6	5
Not remarkable		5	8	3	1
Increased eosinophilic body,tubular		0	0	3	4
minimal		0	0	3	0
mild		0	0	0	4
Liver					
Number examined		5	3	1	5
Not remarkable		5	3	1	4
Cell infiltration,centrilobular		0	0	0	1
minimal		0	0	0	1
Lung(bronchus)					
Number examined		5	3	1	5
Not remarkable		4	3	0	3
Cell infiltration		0	0	0	1
mild		0	0	0	1
Aggregation,alveolar macrophage		1	0	1	1
minimal		1	0	1	1
Lymph node,mesenteric					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Lymph node,submandibular					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Pancreas					
Number examined		5	3	1	5
Not remarkable		5	2	1	4
Atrophy,acinar		0	0	0	1
minimal		0	0	0	1
Fibrosis,islet		0	1	0	0
mild		0	1	0	0
Parathyroid					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Pituitary					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Prostate					
Number examined		5	3	1	5
Not remarkable		2	0	1	3
Cell infiltration,interstitial		3	3	0	2
minimal		3	3	0	2
Salivary gland,submandibular					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Sciatic nerve					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Seminal vesicle(coagulating gland)					
Number examined		5	3	1	5
Not remarkable		5	3	1	5

M : Male

Table 10-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	M	M	M	M
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	7	12	12	7
Skeletal muscle,femoral					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Spinal cord,thoracic					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Spleen					
Number examined		5	3	1	5
Not remarkable		4	1	0	3
Hematopoiesis,extramedullary		1	2	1	2
minimal		1	2	1	1
mild		0	0	0	1
Stomach					
Number examined		5	8	6	5
Not remarkable		4	8	6	0
Erosion		1	0	0	0
minimal		1	0	0	0
Hyperplasia,mucosal,glandular stomach		0	0	0	5
minimal		0	0	0	2
mild		0	0	0	3
Hyperplasia,squamous,limiting ridge		0	0	0	5
minimal		0	0	0	1
mild		0	0	0	4
Testis					
Number examined		5	3	1	5
Not remarkable		3	3	1	4
Atrophy,seminiferous tubular		2	0	0	1
minimal		2	0	0	0
mild		0	0	0	1
Thymus					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Thyroid					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Trachea					
Number examined		5	3	1	5
Not remarkable		5	3	1	5
Urinary bladder					
Number examined		5	8	6	5
Not remarkable		5	8	6	4
Hyperplasia,transitional,diffuse		0	0	0	1
mild		0	0	0	1
Skin,inguinal					
Number examined		0	0	0	2
Not remarkable		0	0	0	2
Kidney(alpha2u globulin)					
Number examined		1	0	1	1
Alpha2u globulin IHC:positive		1	0	1	1
present		1	0	1	1
Kidney(PAS stain)					
Number examined		1	0	1	1
PAS reaction negative		1	0	1	1
present		1	0	1	1

M : Male

Table 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs	Sex:	F	F
	Dose(mg/kg):	0	1000
Findings	Number:	5	5
Adrenal			
Number examined		5	5
Not remarkable		5	5
Bone+Bone marrow,femoral			
Number examined		5	5
Not remarkable		5	5
Cerebellum(Pons)			
Number examined		5	5
Not remarkable		5	5
Cerebrum			
Number examined		5	5
Not remarkable		5	5
Eye			
Number examined		5	5
Not remarkable		5	5
Heart			
Number examined		5	5
Not remarkable		5	5
Intestine,duodenum			
Number examined		5	5
Not remarkable		5	5
Intestine,jejunum			
Number examined		5	5
Not remarkable		5	5
Intestine,ileum(Peyer's patch)			
Number examined		5	5
Not remarkable		5	5
Intestine,cecum			
Number examined		5	5
Not remarkable		5	1
Hyperplasia,mucosal,diffuse		0	4
minimal		0	4
Intestine,colon			
Number examined		5	5
Not remarkable		5	5
Intestine,rectum			
Number examined		5	5
Not remarkable		5	3
Hyperplasia,mucosal,diffuse		0	2
minimal		0	2
Kidney			
Number examined		5	5
Not remarkable		5	5
Liver			
Number examined		5	5
Not remarkable		5	5

F : Female

Table 10-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 5	F 1000 5
Lung(bronchus)			
Number examined		5	5
Not remarkable		4	4
Cell infiltration		1	0
minimal		1	0
Aggregation,alveolar macrophage		0	1
minimal		0	1
Lymph node,mesenteric			
Number examined		5	5
Not remarkable		5	5
Lymph node,submandibular			
Number examined		5	5
Not remarkable		5	5
Ovary			
Number examined		5	5
Not remarkable		5	5
Pancreas			
Number examined		5	5
Not remarkable		5	5
Parathyroid			
Number examined		5	5
Not remarkable		5	5
Pituitary			
Number examined		5	5
Not remarkable		5	4
Cyst		0	1
mild		0	1
Salivary gland,submandibular			
Number examined		5	5
Not remarkable		5	5
Sciatic nerve			
Number examined		5	5
Not remarkable		5	5
Skeletal muscle,femoral			
Number examined		5	5
Not remarkable		5	5
Spinal cord,thoracic			
Number examined		5	5
Not remarkable		5	5
Spleen			
Number examined		5	5
Not remarkable		3	5
Hematopoiesis,extramedullary		2	0
minimal		2	0
Stomach			
Number examined		5	5
Not remarkable		4	0
Hyperplasia,mucosal,glandular stomach		0	4
minimal		0	2
mild		0	2

F : Female

Table 10-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (D42))

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 5	F 1000 5
Stomach (continued)			
Bulla formation,limiting ridge		1	0
minimal		1	0
Hyperplasia,squamous,limiting ridge		0	5
mild		0	5
Thymus			
Number examined		5	5
Not remarkable		5	5
Thyroid			
Number examined		5	5
Not remarkable		5	5
Trachea			
Number examined		5	5
Not remarkable		5	5
Urinary bladder			
Number examined		5	5
Not remarkable		5	2
Hyperplasia,transitional,diffuse		0	3
minimal		0	2
mild		0	1
Uterus			
Number examined		5	5
Not remarkable		5	5
Vagina			
Number examined		5	5
Not remarkable		5	5
Skin,inguinal			
Number examined		0	5
Not remarkable		0	5

F : Female

Table 10-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	11	9	11	12
Adrenal					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Bone+Bone marrow,femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebellum(Pons)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Cerebrum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Eye					
Number examined		5	0	0	5
Not remarkable		4	0	0	5
Dysplasia,retinal		1	0	0	0
mild		1	0	0	0
Heart					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,duodenum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,jejunum					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,ileum(Peyer's patch)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Intestine,cecum					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Intestine,colon					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Intestine,rectum					
Number examined		5	5	5	5
Not remarkable		5	5	5	4
Hyperplasia,mucosal,diffuse		0	0	0	1
minimal		0	0	0	1
Kidney					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Liver					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

Table 10-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 11	F 40 9	F 200 11	F 1000 12
Lung(bronchus)					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Lymph node,mesenteric					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Lymph node,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Ovary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pancreas					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Parathyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Pituitary					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Salivary gland,submandibular					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Sciatic nerve					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Skeletal muscle,femoral					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spinal cord,thoracic					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Spleen					
Number examined		5	0	0	5
Hematopoiesis,extramedullary		5	0	0	5
minimal		2	0	0	1
mild		3	0	0	4
Stomach					
Number examined		5	5	5	5
Not remarkable		5	5	5	1
Erosion		0	0	0	2
minimal		0	0	0	2
Arteritis		0	0	0	1
minimal		0	0	0	1
Hyperplasia,mucosal,glandular stomach		0	0	0	3
minimal		0	0	0	2
mild		0	0	0	1
Hyperplasia,squamous,limiting ridge		0	0	0	4
minimal		0	0	0	2
mild		0	0	0	2

F : Female

Table 10-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of administration period (L4))

Organs	Sex:	F	F	F	F
	Dose(mg/kg):	0	40	200	1000
Findings	Number:	11	9	11	12
Thymus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Thyroid					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Trachea					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Urinary bladder					
Number examined		5	5	5	5
Not remarkable		5	5	5	4
Hyperplasia,transitional,diffuse		0	0	0	1
mild		0	0	0	1
Uterus					
Number examined		5	0	0	5
Not remarkable		5	0	0	5
Vagina					
Number examined		5	0	0	5
Not remarkable		5	0	0	5

F : Female

Table 10-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of recovery period)

Organs	Sex:	M	M
	Dose(mg/kg):	0	1000
Findings	Number:	5	5
Intestine,cecum			
Number examined		5	5
Not remarkable		5	5
Intestine,colon			
Number examined		5	5
Not remarkable		5	5
Intestine,rectum			
Number examined		5	5
Not remarkable		5	5
Kidney			
Number examined		5	5
Not remarkable		5	4
Increased eosinophilic body,tubular		0	1
minimal		0	1
Stomach			
Number examined		5	5
Not remarkable		5	3
Hyperplasia,squamous,limiting ridge		0	2
mild		0	2
Testis			
Number examined		0	3
Not remarkable		0	2
Atrophy,seminiferous tubular		0	1
minimal		0	1
Urinary bladder			
Number examined		5	5
Not remarkable		5	3
Hyperplasia,transitional,diffuse		0	2
minimal		0	1
mild		0	1

M : Male

Table 10-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (End of recovery period)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 0 5	F 1000 5
Intestine,cecum			
Number examined		5	5
Not remarkable		5	4
Cell infiltration,mucosal		0	1
minimal		0	1
Intestine,colon			
Number examined		5	5
Not remarkable		5	5
Intestine,rectum			
Number examined		5	5
Not remarkable		5	5
Kidney			
Number examined		0	1
Not remarkable		0	0
Liver			
Number examined		0	1
Erythrophagia,Kupffer cell		0	1
mild		0	1
Stomach			
Number examined		5	5
Not remarkable		4	4
Erosion		1	0
minimal		1	0
Hyperplasia,squamous,limiting ridge		0	1
minimal		0	1
Urinary bladder			
Number examined		5	5
Not remarkable		5	3
Cell infiltration,submucosal		0	1
mild		0	1
Basophilic materials,lumina		0	1
minimal		0	1
Hyperplasia,transitional,diffuse		0	1
minimal		0	1
PAPILLOMA,transitional cell		0	1
present		0	1
Tissue around the urethral orifice			
Number examined		0	1
Inflammation		0	1
mild		0	1
Basophilic materials,urethral lumina		0	1
minimal		0	1
Hyperplasia,squamous,urethra,diffuse		0	1
mild		0	1

F : Female

Table 10-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (Undelivered)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F 40 3	F 200 1
Adrenal			
Number examined		3	1
Not remarkable		3	1
Bone+Bone marrow,femoral			
Number examined		3	1
Not remarkable		3	1
Cerebellum(Pons)			
Number examined		3	1
Not remarkable		3	1
Cerebrum			
Number examined		3	1
Not remarkable		3	1
Eye			
Number examined		3	1
Not remarkable		3	1
Heart			
Number examined		3	1
Not remarkable		2	1
Cell infiltration,interstitial		1	0
minimal		1	0
Intestine,duodenum			
Number examined		3	1
Not remarkable		3	1
Intestine,jejunum			
Number examined		3	1
Not remarkable		3	1
Intestine,ileum(Peyer's patch)			
Number examined		3	1
Not remarkable		3	1
Intestine,cecum			
Number examined		3	1
Not remarkable		3	1
Intestine,colon			
Number examined		3	1
Not remarkable		3	1
Intestine,rectum			
Number examined		3	1
Not remarkable		3	1
Kidney			
Number examined		3	1
Not remarkable		3	1
Liver			
Number examined		3	1
Not remarkable		3	1
Lung(bronchus)			
Number examined		3	1
Not remarkable		3	1

F : Female

Table 10-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (Undelivered)

Organs	Sex:	F	F
	Dose(mg/kg):	40	200
Findings	Number:	3	1
Lymph node,mesenteric			
Number examined		3	1
Not remarkable		3	1
Lymph node,submandibular			
Number examined		3	1
Not remarkable		3	1
Ovary			
Number examined		3	1
Not remarkable		3	1
Pancreas			
Number examined		3	1
Not remarkable		3	1
Parathyroid			
Number examined		3	1
Not remarkable		3	1
Pituitary			
Number examined		3	1
Not remarkable		3	1
Salivary gland,submandibular			
Number examined		3	1
Not remarkable		3	1
Sciatic nerve			
Number examined		3	1
Not remarkable		3	1
Skeletal muscle,femoral			
Number examined		3	1
Not remarkable		3	1
Spinal cord,thoracic			
Number examined		3	1
Not remarkable		3	1
Spleen			
Number examined		3	1
Not remarkable		0	1
Hematopoiesis,extramedullary		3	0
minimal		3	0
Stomach			
Number examined		3	1
Not remarkable		3	1
Thymus			
Number examined		3	1
Not remarkable		3	1
Thyroid			
Number examined		3	1
Not remarkable		3	1
Trachea			
Number examined		3	1
Not remarkable		3	1

F : Female

Table 10-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (Undelivered)

Organs	Sex:	F	F
	Dose(mg/kg):	40	200
Findings	Number:	3	1
Urinary bladder			
Number examined		3	1
Not remarkable		3	1
Uterus			
Number examined		3	1
Not remarkable		3	1
Vagina			
Number examined		3	1
Not remarkable		3	1

F : Female

Table 10-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (All littermates died)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F / 0 / 1
Adrenal		
Number examined		1
Not remarkable		1
Bone+Bone marrow,femoral		
Number examined		1
Hematopoiesis,increased		1
mild		1
Cerebellum(Pons)		
Number examined		1
Not remarkable		1
Cerebrum		
Number examined		1
Not remarkable		1
Eye		
Number examined		1
Not remarkable		1
Heart		
Number examined		1
Not remarkable		1
Intestine,duodenum		
Number examined		1
Not remarkable		1
Intestine,jejunum		
Number examined		1
Not remarkable		1
Intestine,ileum(Peyer's patch)		
Number examined		1
Not remarkable		1
Intestine,cecum		
Number examined		1
Not remarkable		1
Intestine,colon		
Number examined		1
Not remarkable		1
Intestine,rectum		
Number examined		1
Not remarkable		1
Kidney		
Number examined		1
Not remarkable		1
Liver		
Number examined		1
Not remarkable		1
Lung(bronchus)		
Number examined		1
Not remarkable		1

F : Female

Table 10-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (All littermates died)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	F / 0 / 1
Lymph node,mesenteric		
Number examined		1
Not remarkable		1
Lymph node,submandibular		
Number examined		1
Not remarkable		1
Ovary		
Number examined		1
Atrophy		1
mild		1
Pancreas		
Number examined		1
Not remarkable		1
Parathyroid		
Number examined		1
Not remarkable		1
Pituitary		
Number examined		1
Not remarkable		1
Salivary gland,submandibular		
Number examined		1
Hypertrophy,acinar cell		1
mild		1
Sciatic nerve		
Number examined		1
Not remarkable		1
Skeletal muscle,femoral		
Number examined		1
Not remarkable		1
Spinal cord,thoracic		
Number examined		1
Not remarkable		1
Spleen		
Number examined		1
Hematopoiesis,extramedullary		1
mild		1
Stomach		
Number examined		1
Not remarkable		1
Thymus		
Number examined		1
Atrophy		1
minimal		1
Thyroid		
Number examined		1
Not remarkable		1
Trachea		
Number examined		1
Not remarkable		1

F : Female

Table 10-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Histopathological findings (All littermates died)

Organs	Sex:	F
	Dose(mg/kg):	0
Findings	Number:	1
Urinary bladder		
Number examined		1
Not remarkable		1
Uterus		
Number examined		1
Inflammation		1
mild		1
Vagina		
Number examined		1
Not remarkable		1

F : Female

Table 11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Estrous cycle in female rats during the pre-mating period (Main group)

Dose mg/kg	No. of animals	Count of estrus						Mean duration of cycles Mean±S.D.	Index of animals with abnormal estrous cycle (%)a)
		0	1	2	3	4	Mean±S.D.		
0	12	0	0	0	4	8	3.7±0.5	4.2±0.3	0/12(0.0)
40	12	0	0	0	5	7	3.6±0.5	4.3±0.5	1/12(8.3)
200	12	0	0	1	7	4	3.3±0.6	4.3±0.6	1/12(8.3)
1000	12	0	0	0	7	5	3.4±0.5	4.1±0.3	0/12(0.0)

a): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
No significant difference in any treated groups from control group.

Table 12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Mating and fertility of animals

	Male				Female			
Dose mg/kg	No. of males	Days until copulation Mean±S.D.	Copulation index (%) a)	Insemination index (%) b)	No. of females	Days until copulation Mean±S.D.	Copulation index (%) a)	Fertility index (%) c)
0	12	2.6±1.6	12/12(100.0)	12/12(100.0)	12	2.6±1.6	12/12(100.0)	12/12(100.0)
40	12	2.3±1.3	11/12(91.7)	9/11(81.8)	12	2.3±1.3	11/12(91.7)	9/11(81.8)
200	12	2.1±1.2	12/12(100.0)	11/12(91.7)	12	2.1±1.2	12/12(100.0)	11/12(91.7)
1000	12	2.2±1.6	12/12(100.0)	12/12(100.0)	12	2.2±1.6	12/12(100.0)	12/12(100.0)

a): (No. of copulated animals / No. of mated animals)×100
b): (No. of males which impregnated females / No. of copulated males)×100
c): (No. of pregnant females / No. of copulated females)×100
No significant difference in any treated groups from control group.

Table 13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with liveborns	Gestation index % a)	Gestation length in days	No. of corpora lutea	No. of implan-tation sites	Implan-tation index % b)	Delivery index % c)	No. of still-borns (%)d)	No. of live-borns	External e) abnor-malities(%)f)
	Total	12	11	91.7		171	158			1	145	0
0	Mean				22.0	14.3	13.2	88.3	93.1	(8.3)	12.1	(0.0)
	S.D.				0.9	3.4	4.2	22.1	10.2	(28.9)	4.3	(0.0)
	Total	9	9	100.0		148	145			1	128	0
40	Mean				21.9	16.4	16.1*	97.8	89.4	(0.7)	14.2	(0.0)
	S.D.				0.3	1.5	1.8ST	3.3	18.7	(2.2)	3.1	(0.0)
	Total	11	11	100.0		179	179			1	165	0
200	Mean				21.7	16.3	16.3*	100.0*	92.4	(0.8)	15.0	(0.0)
	S.D.				0.5	1.6	1.6ST	0.0ST	5.6	(2.5)	2.4	(0.0)
	Total	12	12	100.0		195	193			3	180	0
1000	Mean				21.8	16.3	16.1*	99.1	94.8	(1.7)	15.0	(0.0)
	S.D.				0.4	1.5	1.2ST	2.1	6.1	(3.1)	1.7	(0.0)

a): (No. of females which delivered liveborns / No. of pregnant females)×100
b): (No. of implantation sites / No. of corpora lutea)×100
c): (No. of delivered pups / No. of implantation sites)×100
d): (No. of stillborns / No. of delivered pups)×100
e): No. of delivered pups with external abnormalities
f): (No. of delivered pups with external abnormalities / No. of delivered pups)×100
*: $p<0.05$ (Significant difference from control group)
ST: Steel's test

Table 14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Viability index of pups

Dose mg/kg		No. of dams	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of dams	No. of live pups		Viability index on postnatal day 4 % b)
							Day 0	Day 4	
	Total	12	145	146		11	145	143	
0	Mean		12.1	12.2	91.7		13.2	13.0	98.5
	S.D.		4.3	4.1	28.9		2.2	2.3	3.5
	Total	9	128	129		9	128	125	
40	Mean		14.2	14.3	99.3		14.2	13.9	98.0
	S.D.		3.1	3.1	2.2		3.1	2.9	4.4
	Total	11	165	166		11	165	161	
200	Mean		15.0	15.1	99.2		15.0	14.6	97.7
	S.D.		2.4	2.2	2.5		2.4	2.2	4.5
	Total	12	180	183		12	180	179	
1000	Mean		15.0	15.3	98.3		15.0	14.9	99.5
	S.D.		1.7	1.5	3.1		1.7	1.7	1.8

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100
No significant difference in any treated groups from control group.

Table 15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Sex ratio of pups

Dose mg/kg	No. of dams		Liveborns No. of males	Liveborns No. of females	Stillborns No. of males	Stillborns No. of females	Sex ratio of delivered pups a)	Sex ratio of liveborns b)	No. of dams	Postnatal day 4 No. of males	Postnatal day 4 No. of females	Sex ratio of live pups on day 4 c)
		Total	68	77	1	0				68	75	
0	12	Mean	5.7	6.4	0.1	0.0	0.52	0.47	11	6.2	6.8	0.48
		S.D.	2.3	2.8	0.3	0.0	0.18	0.10		1.5	2.2	0.11
		Total	64	64	1	0				61	64	
40	9	Mean	7.1	7.1	0.1	0.0	0.51	0.50	9	6.8	7.1	0.49
		S.D.	2.2	2.2	0.3	0.0	0.10	0.10		1.7	2.2	0.09
		Total	87	78	0	1				84	77	
200	11	Mean	7.9	7.1	0.0	0.1	0.54	0.54	11	7.6	7.0	0.54
		S.D.	1.9	3.3	0.0	0.3	0.16	0.17		1.7	3.2	0.17
		Total	86	94	2	1				86	93	
1000	12	Mean	7.2	7.8	0.2	0.1	0.48	0.48	12	7.2	7.8	0.48
		S.D.	2.4	2.2	0.4	0.3	0.13	0.14		2.4	2.3	0.14

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4
No significant difference in any treated groups from control group.

Table 16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Body weight of pups

Dose mg/kg		Male			Female		
		0	4a)	Gain	0	4a)	Gain
0	No.	11	11	11	11	11	11
	Mean	6.6	10.7	4.1	6.2	10.0	3.8
	S.D.	0.6	1.4	0.9	0.6	1.5	1.0
40	No.	9	9	9	9	9	9
	Mean	6.6	10.2	3.6	6.2	9.7	3.5
	S.D.	0.5	1.6	1.3	0.5	1.6	1.2
200	No.	11	11	11	11	11	11
	Mean	6.5	9.8	3.3	6.2	9.3	3.2
	S.D.	0.4	1.2	1.0	0.4	1.3	1.0
1000	No.	12	12	12	12	12	12
	Mean	6.8	10.2	3.5	6.4	9.8	3.4
	S.D.	0.5	0.9	0.6	0.5	0.9	0.6

Unit: g
No.: No. of dams
a): Postnatal day
No significant difference in any treated groups from control group.

Table 17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Externally for gross abnormalities in dead pups

Dose (mg/kg)	0	40	200	1000
Male				
No. of pups examined	0	1	3	0
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	2	0	1	0
No. of pups with abnormal findings	0	0	0	0

Table 18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Externally for gross abnormalities in pups on postnatal day 4

Dose (mg/kg)	0	40	200	1000
Male				
No. of pups examined	68	61	84	86
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	75	64	77	93
No. of pups with abnormal findings	0	0	0	0

Appendix 1-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
1001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings

Appendix 1-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 40

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2001	-	-	-	-	-	-	-	B	B	-	-	-	-	-
2002	-	-	B	B	-	-	-	B	B	-	-	-	-	B
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	B	-	-	-	-	-	B	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	B	B	-	-	-	B	-	-	-
2010	-	-	-	B	B	-	B	-	B	-	-	-	B	-
2011	-	-	-	-	-	-	-	B	-	B	-	B	-	-
2012	-	-	B	-	-	-	-	-	B	-	B	-	-	-

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 40

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2002	B	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2006	-	-	-	-	-	B	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	B	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	B	-	-	-	-	-
2011	-	-	-	-	-	-	B	-	-	-	-	-	-	-
2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 40

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
2001	-	-	-	-	-	-	-	B	-	-	-	B	-	-	-
2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2005	-	-	-	-	-	-	-	-	B	-	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	B	B	-	B	-	B	-	-
2011	-	-	-	-	-	-	-	-	-	-	-	-	B	-	B
2012	-	-	-	-	-	-	-	-	B	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 200

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3001	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3002	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3003	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3004	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3005	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3006	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3007	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3008	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3009	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3010	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3011	-	B	B	B	B	B	B	B	B	B	B	B	B	B
3012	-	B	B	B	B	B	B	B	B	B	B	B	B	B

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 200

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
3001	B	-	-	-	B	B	B	B	B	B	B	B	B	B
3002	B	-	-	B	B	B	B	B	B	B	B	B	B	B
3003	B	-	-	B	B	B	B	B	B	B	B	B	B	B
3004	B	-	B	B	B	B	B	B	B	B	B	B	B	B
3005	B	-	B	B	B	B	B	B	B	B	B	B	B	B
3006	B	-	B	B	B	B	B	B	B	B	B	B	B	B
3007	B	-	-	-	B	B	B	B	B	B	B	B	B	B
3008	B	-	-	B	B	B	B	B	B	B	B	B	B	B
3009	B	-	B	B	B	B	B	B	B	B	B	B	B	B
3010	B	-	B	B	B	B	B	B	B	B	B	B	B	B
3011	B	-	-	-	-	B	B	B	B	B	B	B	B	B
3012	B	-	-	-	-	B	B	B	B	B	B	B	B	B

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 200

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
3001	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3002	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3003	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3004	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3005	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3006	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3007	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3008	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3009	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3010	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3011	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3012	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B

a): Day of necropsy
B: Colored feces (dark blue)

Appendix 1-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4001	A	B	B	B	B	B	B	B	AB	AB	B	AB	B	AB
4002	A	AB	B	B	AB	B	AB	AB	B	AB	B	B	AB	B
4003	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4004	-	AB	AB	B	B	B	B	B	B	B	B	B	B	B
4005	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4006	-	AB	B	B	B	B	B	B	AB	B	B	B	B	B
4007	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4008	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4009	-	B	B	AB	AB	AB	B	AB	B	B	B	B	B	B
4010	-	B	B	B	B	B	B	BD	ABD	BD	ABD	BD	BD	BD
4011	A	B	B	B	AB	B	B	B	B	B	B	B	AB	B
4012	A	AB	AB	B	B	AB	B	B	B	B	AB	B	AB	AB

-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)
D: Fracture of incisors

Appendix 1-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
4001	B	-	B	B	B	B	AB	AB	AB	B	B	B	B	B
4002	AB	-	-	-	-	-	-	AB	AB	B	B	AB	AB	B
4003	B	-	-	-	-	B	B	B	B	B	B	B	B	B
4004	AB	-	B	B	B	B	B	B	B	B	B	B	AB	B
4005	B	-	B	B	B	B	B	B	B	B	B	B	B	B
4006	B	-	-	B	B	B	B	B	B	B	B	B	B	B
4007	B	-	B	B	B	B	B	B	B	B	B	B	B	B
4008	B	-	B	B	B	B	B	B	B	B	B	B	B	B
4009	B	-	-	B	B	B	B	B	B	B	B	B	B	B
4010	BD	D	D	BD	B	B	B	B	B	B	B	B	B	B
4011	B	-	B	B	B	B	B	AB	B	B	B	B	B	AB
4012	AB	-	-	-	-	B	B	AB	AB	AB	AB	B	B	AB

-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)
D: Fracture of incisors

Appendix 1-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
4001	AB	B	B	B	B	B	AB	B	B	B	B	B	AB	AB	AB
4002	B	AB	B	B	B	AB	AB	AB	AB	AB	B	B	B	AB	AB
4003	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4004	AB	B	B	AB	AB	B	B	B	B	B	B	B	B	B	AB
4005	B	B	AB	B	B	B	B	B	B	B	B	B	B	B	B
4006	B	B	AB	AB	AB	B	B	AB	B	B	B	B	B	B	AB
4007	B	B	AB	AB	B	B	B	B	B	B	B	B	B	B	B
4008	AB	B	B	B	B	B	B	B	B	B	B	B	B	B	
4009	B	B	B	B	B	B	AB	B	B	B	B	AB	B	B	
4010	B	B	B	B	B	B	B	AB	B	B	B	B	B	B	
4011	B	B	AB	B	B	B	B	B	AB	B	B	B	B	B	
4012	B	AB	B	B	AB	B	AB	AB	B	B	AB	AB	AB	AB	

a): Day of necropsy
A: Colored urine (light purple)
B: Colored feces (dark blue)

Appendix 1-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 40

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2102	-	-	-	-	-	-	-	-	-	-	B	-	-	-	-
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2104	-	-	-	-	B	-	-	B	B	-	-	-	-	-	-
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2108	-	-	-	-	-	-	-	B	-	B	-	-	-	-	-
2109	-	-	-	-	-	-	-	-	-	B	-	-	-	-	-
2110	-	-	B	B	-	-	-	-	B	-	-	-	-	-	-
2111	-	-	-	-	-	-	-	B	B	-	-	B	-	-	-
2112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 200

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3101	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3102	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3103	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3104	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3105	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3106	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3107	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3108	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3109	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3110	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3111	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
3112	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B

-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats during the pre-mating period (Main group)
Dose (mg/kg): 1000

Animal number	Day of administration														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4101	A	B	B	B	B	B	B	AB	B	B	B	B	B	B	AB
4102	-	B	B	B	B	B	B	B	B	B	AB	B	B	B	B
4103	-	B	B	B	B	B	AB	B	B	AB	B	B	B	B	B
4104	A	B	B	B	AB	B	B	B	B	B	B	B	B	B	AB
4105	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4106	-	B	B	B	B	B	AB	B	AB	B	B	B	B	B	B
4107	-	B	B	B	B	B	B	B	B	B	AB	AB	B	B	B
4108	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4109	-	B	B	B	B	B	B	AB	B	B	B	B	B	B	B
4110	-	AB	B	B	B	B	B	B	B	B	B	B	B	B	B
4111	A	B	B	B	B	B	B	AB	B	AB	AB	B	B	B	B
4112	A	B	AB	AB	B	B	B	B	B	B	B	B	B	B	AB

-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)

Appendix 1-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)
1101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
1102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d			
1103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
1104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
1105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
1107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	cd	d
1108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
1109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
1110	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d			
1111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d	
1112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d			

a): Gestation day
-: No abnormal findings
cd: Continuation of delivery
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 40

Dam number	Administration																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)
2101	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2104	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2105	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2106	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2107	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	d		
2108	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d			
2109	Non-pregnant																								
2110	Non-pregnant																								
2111	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-/d		
2112	Not copulated																								

a): Gestation day
-: No abnormal findings
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 200

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)
3101	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3102	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3103	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3104	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B/d		
3105	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B/d			
3106	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B/d			
3107	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3108	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3109	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3110	Non-pregnant																								
3111	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
3112	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B/d			

a): Gestation day
-: No abnormal findings
B: Colored feces (dark blue)
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the gestation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24a)
4101	-	B	B	B	B	B	AB	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4102	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4103	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4104	-	B	AB	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B/d			
4105	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4106	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4107	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4108	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4109	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4110	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d			
4111	-	AB	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		
4112	-	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	d		

a): Gestation day
-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)
d: Delivery
/d: Found delivery after the observation of general conditions.

Appendix 1-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration					
	0	1	2	3	4a)	5b)
1101	-	-	-	-	-	-
1102	-	-	-	-	-	-
1103	-	-	-	-	-	-
1104	-	-	-	-	-	-
1105	-	-	-	-	-	-
1106	-	-	-	-	-	-
1107c)	G					
1108	-	-	-	-	-	-
1109	-	-	-	-	-	-
1110	-	-	-	-	-	-
1111	-	-	-	-	-	-
1112	-	-	-	-	-	-

a): Lactation day
b): Day of necropsy
c): Necropsied on lactation day 0 because all pups were stillborn
-: No abnormal findings
G: Vaginal prolapse

Appendix 1-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 40

Dam number	Administration					
	0	1	2	3	4a)	5b)
2101	-	-	-	-	-	-
2102	-	-	-	-	-	-
2103	-	-	-	-	-	-
2104	-	-	-	-	-	-
2105	-	-	-	-	-	-
2106	-	-	-	-	-	-
2107	-	-	-	-	-	-
2108	-	B	B	B	B	B
2109	Non-pregnant					
2110	Non-pregnant					
2111	-	-	-	-	-	-
2112	Not copulated					

a): Lactation day
b): Day of necropsy
-: No abnormal findings
B: Colored feces (dark blue)

Appendix 1-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 200

Dam number	Administration					
	0	1	2	3	4a)	5b)
3101	B	B	B	B	B	B
3102	B	B	B	B	B	B
3103	B	B	B	B	B	B
3104	B	B	B	B	B	B
3105	B	B	B	B	B	B
3106	B	B	B	B	B	B
3107	B	B	B	B	B	B
3108	B	B	B	B	B	B
3109	B	B	B	B	B	B
3110	Non-pregnant					
3111	B	B	B	B	B	B
3112	B	B	B	B	B	B

a): Lactation day
b): Day of necropsy
B: Colored feces (dark blue)

Appendix 1-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in dams during the lactation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration					
	0	1	2	3	4a)	5b)
4101	B	B	B	B	B	B
4102	B	B	B	B	B	B
4103	B	B	B	B	B	B
4104	B	B	B	B	B	B
4105	B	B	B	B	B	B
4106	B	B	B	B	B	B
4107	B	B	B	B	B	B
4108	B	B	B	B	B	B
4109	B	B	B	B	B	B
4110	B	B	B	B	B	B
4111	B	B	B	B	B	B
4112	B	B	B	B	B	B

a): Lactation day
b): Day of necropsy
B: Colored feces (dark blue)

Appendix 1-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-: No abnormal findings

Appendix 1-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
1113	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1114	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1115	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1116	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1117	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

a): Day of necropsy
-: No abnormal findings

Appendix 1-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4113	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4114	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4115	-	B	B	B	B	B	B	B	B	B	B	AB	B	B
4116	-	B	B	B	B	B	B	B	B	AB	B	B	B	B
4117	-	B	B	B	B	B	B	B	B	B	B	B	B	B
4118	-	B	B	AB	B	B	B	B	B	B	B	B	B	B
4119	-	AB	B	AB	B	B	B	B	B	B	B	B	B	B
4120	A	B	B	AB	B	B	B	B	B	B	B	B	B	B
4121	-	B	B	B	B	B	B	BE	BE	BE	BE	BE	BE	BE
4122	-	AB	B	B	B	B	B	B	B	B	B	B	B	B

-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)
E: Swelling, around the urethral orifice

Appendix 1-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
4113	B	B	B	B	B	B	B	AB	B	B	B	B	B	B
4114	B	B	AB	B	B	B	B	B	B	B	B	B	B	B
4115	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4116	B	B	B	AB	B	B	B	B	B	B	B	B	B	B
4117	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4118	AB	B	AB	B	B	B	B	B	B	B	AB	B	B	AB
4119	B	B	B	B	B	B	B	B	AB	B	B	B	B	AB
4120	B	B	B	B	B	B	B	AB	B	B	B	B	B	B
4121	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE
4122	B	B	B	B	B	B	B	B	B	B	B	B	B	B

A: Colored urine (light purple)
B: Colored feces (dark blue)
E: Swelling, around the urethral orifice

Appendix 1-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Satellite group, Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration														
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43a)
4113	B	B	B	B	B	B	B	B	B	B	B	B	B	B	AB
4114	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4115	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4116	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4117	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
4118	B	B	B	B	B	B	B	B	B	B	B	B	B	B	
4119	B	B	B	B	BF	BF	BF	BF	BF	BF	BF	BF	BF	BF	
4120	B	B	B	B	BF	BF	BF	BF	BF	BF	BF	BF	BF	BF	
4121	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	BE	
4122	B	B	B	B	B	B	BF	BF	BF	BF	BF	BF	BF	BF	

a): Day of necropsy
A: Colored urine (light purple)
B: Colored feces (dark blue)
E: Swelling, around the urethral orifice
F: Discoloration of skin, blue, systemic

Appendix 1-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
1008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in male rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
4008	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4009	B	B	-	-	-	-	-	-	-	-	-	-	-	-	-
4010	AB	B	-	-	-	-	-	-	-	-	-	-	-	-	-
4011	B	B	-	-	-	-	-	-	-	-	-	-	-	-	-
4012	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)

Appendix 1-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
1118	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1119	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1121	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings

Appendix 1-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual clinical signs in female rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
4118	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4119	ABF	F	F	F	F	-	-	-	-	-	-	-	-	-	-
4120	BF	F	F	-	-	-	-	-	-	-	-	-	-	-	-
4121	BE	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4122	BF	F	F	-	-	-	-	-	-	-	-	-	-	-	-

a): Day of necropsy
-: No abnormal findings
A: Colored urine (light purple)
B: Colored feces (dark blue)
E: Swelling, around the urethral orifice
F: Discoloration of skin, blue, systemic

Appendix 2-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
									NP	NP		NC
Posture a)	N	N	N	N	N	N	N	N			N	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NC: Not copulated
NP: Non-pregnant

Appendix 2-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Posture a)	N	N	N	N	N	N	N	N	N		N	N
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NP: Non-pregnant

Appendix 2-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 1)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Posture a)	N	N	N	N	N	N	N	N			N	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NC: Not copulated
NP: Non-pregnant

Appendix 2-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Posture a)	N	N	N	N	N	N	N	N	N		N	N
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NP: Non-pregnant

Appendix 2-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 7)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
									NP	NP		NC
Posture a)	N	N	N	N	N	N	N	N			N	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NC: Not copulated
NP: Non-pregnant

Appendix 2-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Posture a)	N	N	N	N	N	N	N	N	N		N	N
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NP: Non-pregnant

Appendix 2-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 14)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Posture a)	N	N	N	N	N	N	N	N			N	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NC: Not copulated
NP: Non-pregnant

Appendix 2-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Posture a)	N	N	N	N	N	N	N	N	N		N	N
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NP: Non-pregnant

Appendix 2-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Gestation day 20)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-49 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7 d)	8	9	10	11	12
Posture a)	N	N	N	N	N	N		N	N	N	N	N
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) Necropsied on lactation day 0 because all pups were stillborn

Appendix 2-50 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Posture a)	N	N	N	N	N	N	N	N			N	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NC: Not copulated
NP: Non-pregnant

Appendix 2-51 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Posture a)	N	N	N	N	N	N	N	N	N		N	N
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
NP: Non-pregnant

Appendix 2-52 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Main group, Lactation day 4)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Posture a)	N	N	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-53 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-54 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-55 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-56 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-57 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-58 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-59 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-60 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-61 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-62 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-63 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-64 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Posture a)	N	N	N	N	N	N	N	N	N	N
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-65 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-66 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-67 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-68 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-69 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-70 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-71 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-72 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: home cage observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Posture a)	N	N	N	N	N
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0

a) N: Normal, F: Flattened, H: Hunched
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe

Appendix 2-73 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-74 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-75 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-76 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-77 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-78 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-79 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-80 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-81 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-82 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-83 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-84 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-85 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	1	1	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-86 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-87 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	1	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-88 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	1	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-89 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-90 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-91 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-92 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	1	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	1	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	1	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-93 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	1	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-94 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-95 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-96 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-97 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-98 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-99 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-100 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-101 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-102 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-103 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-104 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-105 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-106 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Ease of removal from cage a)	0	0	0	0	0	0	0	0			0	
Fur condition b)	0	0	0	0	0	0	0	0			0	
Skin c)	0	0	0	0	0	0	0	0			0	
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0			0	
Exophthalmos e)	0	0	0	0	0	0	0	0			0	
Palpebral closure f)	0	0	0	0	0	0	0	0			0	
Mucosal membranes g)	0	0	0	0	0	0	0	0			0	
Lacrimation h)	0	0	0	0	0	0	0	0			0	
Piloerection i)	0	0	0	0	0	0	0	0			0	
Pupil size j)	0	0	0	0	0	0	0	0			0	
Salivation k)	0	0	0	0	0	0	0	0			0	
Abnormal respiration l)	0	0	0	0	0	0	0	0			0	
Vocalization m)	0	0	0	0	0	0	0	0			0	
Reactivity to handling n)	0	0	0	0	0	0	0	0			0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NC: Not copulated
NP: Non-pregnant

Appendix 2-107 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	0	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	1	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NP: Non-pregnant

Appendix 2-108 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 1)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	2	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-109 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-110 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Ease of removal from cage a)	0	0	0	0	0	0	0	0			0	
Fur condition b)	0	0	0	0	0	0	0	0			0	
Skin c)	0	0	0	0	0	0	0	0			0	
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0			0	
Exophthalmos e)	0	0	0	0	0	0	0	0			0	
Palpebral closure f)	0	0	0	0	0	0	0	0			0	
Mucosal membranes g)	0	0	0	0	0	0	0	0			0	
Lacrimation h)	0	0	0	0	0	0	0	0			0	
Piloerection i)	0	0	0	0	0	0	0	0			0	
Pupil size j)	0	0	0	0	0	0	0	0			0	
Salivation k)	0	0	0	0	0	0	0	0			0	
Abnormal respiration l)	0	0	0	0	0	0	0	0			0	
Vocalization m)	0	0	0	0	0	0	0	0			0	
Reactivity to handling n)	0	0	0	0	0	0	0	0			0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NC: Not copulated
NP: Non-pregnant

Appendix 2-111 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	0	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	0	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NP: Non-pregnant

Appendix 2-112 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 7)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	1	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-113 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-114 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Ease of removal from cage a)	0	0	0	0	0	0	0	0			0	
Fur condition b)	0	0	0	0	0	0	0	0			0	
Skin c)	0	0	0	0	0	0	0	0			0	
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0			0	
Exophthalmos e)	0	0	0	0	0	0	0	0			0	
Palpebral closure f)	0	0	0	0	0	0	0	0			0	
Mucosal membranes g)	0	0	0	0	0	0	0	0			0	
Lacrimation h)	0	0	0	0	0	0	0	0			0	
Piloerection i)	0	0	0	0	0	0	0	0			0	
Pupil size j)	0	0	0	0	0	0	0	0			0	
Salivation k)	0	0	0	0	0	0	0	0			0	
Abnormal respiration l)	0	0	0	0	0	0	0	0			0	
Vocalization m)	0	0	0	0	0	0	0	0			0	
Reactivity to handling n)	0	0	0	0	0	0	0	0			0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NC: Not copulated
NP: Non-pregnant

Appendix 2-115 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	0	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	0	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NP: Non-pregnant

Appendix 2-116 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 14)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-117 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-118 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Ease of removal from cage a)	0	0	0	0	0	0	0	0			0	
Fur condition b)	0	0	0	0	0	0	0	0			0	
Skin c)	0	0	0	0	0	0	0	0			0	
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0			0	
Exophthalmos e)	0	0	0	0	0	0	0	0			0	
Palpebral closure f)	0	0	0	0	0	0	0	0			0	
Mucosal membranes g)	0	0	0	0	0	0	0	0			0	
Lacrimation h)	0	0	0	0	0	0	0	0			0	
Piloerection i)	0	0	0	0	0	0	0	0			0	
Pupil size j)	0	0	0	0	0	0	0	0			0	
Salivation k)	0	0	0	0	0	0	0	0			0	
Abnormal respiration l)	0	0	0	0	0	0	0	0			0	
Vocalization m)	0	0	0	0	0	0	0	0			0	
Reactivity to handling n)	0	0	0	0	0	0	0	0			0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NC: Not copulated
NP: Non-pregnant

Appendix 2-119 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	0	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	0	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NP: Non-pregnant

Appendix 2-120 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Gestation day 20)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-121 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7 o)	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Necropsied on lactation day 0 because all pups were stillborn

Appendix 2-122 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Ease of removal from cage a)	0	0	0	0	0	0	0	0			0	
Fur condition b)	0	0	0	0	0	0	0	0			0	
Skin c)	0	0	0	0	0	0	0	0			0	
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0			0	
Exophthalmos e)	0	0	0	0	0	0	0	0			0	
Palpebral closure f)	0	0	0	0	0	0	0	0			0	
Mucosal membranes g)	0	0	0	0	0	0	0	0			0	
Lacrimation h)	0	0	0	0	0	0	0	0			0	
Piloerection i)	0	0	0	0	0	0	0	0			0	
Pupil size j)	0	0	0	0	0	0	0	0			0	
Salivation k)	0	0	0	0	0	0	0	0			0	
Abnormal respiration l)	0	0	0	0	0	0	0	0			0	
Vocalization m)	0	0	0	0	0	0	0	0			0	
Reactivity to handling n)	0	0	0	0	0	0	0	0			0	

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NC: Not copulated
NP: Non-pregnant

Appendix 2-123 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0		0	0
Fur condition b)	0	0	0	0	0	0	0	0	0		0	0
Skin c)	0	0	0	0	0	0	0	0	0		0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0		0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0		0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0		0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0		0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0		0	0
Piloerection i)	0	0	0	0	0	0	0	0	0		0	0
Pupil size j)	0	0	0	0	0	0	0	0	0		0	0
Salivation k)	0	0	0	0	0	0	0	0	0		0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0		0	0
Vocalization m)	0	0	0	0	0	0	0	0	0		0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0		0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
NP: Non-pregnant

Appendix 2-124 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Main group, Lactation day 4)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-125 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-126 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-127 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-128 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-129 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-130 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-131 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	1	0	1	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-132 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	1	0	0	0	1	0	0	0	1
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-133 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-134 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-135 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-136 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0	0	0	0	0	0
Fur condition b)	0	0	0	0	0	0	0	0	0	0
Skin c)	0	0	0	0	0	0	1o)	1o)	0	1o)
Secretions-Eye, Nose d)	0	0	0	0	0	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0	0	0	0	0	0
Lacrimation h)	0	0	0	0	0	0	0	0	0	0
Piloerection i)	0	0	0	0	0	0	0	0	0	0
Pupil size j)	0	0	0	0	0	0	0	0	0	0
Salivation k)	0	0	0	0	0	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0	0	0	0	0	0
Vocalization m)	0	0	0	0	0	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Blue

Appendix 2-137 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-138 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-139 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-140 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-141 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-142 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	1o)	1o)	0	1o)
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult
o) Blue

Appendix 2-143 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-144 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: in-the-hand observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Ease of removal from cage a)	0	0	0	0	0
Fur condition b)	0	0	0	0	0
Skin c)	0	0	0	0	0
Secretions-Eye, Nose d)	0	0	0	0	0
Exophthalmos e)	0	0	0	0	0
Palpebral closure f)	0	0	0	0	0
Mucosal membranes g)	0	0	0	0	0
Lacrimation h)	0	0	0	0	0
Piloerection i)	0	0	0	0	0
Pupil size j)	0	0	0	0	0
Salivation k)	0	0	0	0	0
Abnormal respiration l)	0	0	0	0	0
Vocalization m)	0	0	0	0	0
Reactivity to handling n)	0	0	0	0	0

a) -1: Atypically docile, 0: Easy, 1: Some resistance/avoidance, 2: Difficult, 3: Very difficult
b) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
c) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
d) 0: Absent, 1: Present
e) 0: Absent, 1: Present
f) 0: Normal, 1: Slightly closed, 2: Half closed, 3: Completely closed
g) 0: Normal, 1: Slight, 2: Moderate, 3: Marked
h) 0: Normal, 1: Present
i) 0: Absent, 1: Present
j) -1: Miosis, 0: Normal, 1: Half opened pupil, 2: Mydriasis
k) 0: None, 1: Slight, 2: Moderate, 3: Marked
l) 0: Absent, 1: Slight, 2: Moderate, 3: Marked
m) 0: None, 1: Soft, 2: Moderate, 3: Loud/aggressive
n) -1: Atypically docile, 0: Easy, 1: Slightly awkward, 2: Difficult, 3: Very difficult

Appendix 2-145 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	2	3	0	0	3	6	1	4	0	2
Defecation count	0	0	0	0	0	0	0	0	5	0	0	0
Urination h)	0	0	0	0	0	0	0	0	1	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-146 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	0	2	1	2	1	1	5	4	4	1	3
Defecation count	0	1	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-147 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	2	6	1	2	2	1	4	5	4	6	1
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-148 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	1	3	3	2	2	1	5	3	6	1	0
Defecation count	0	0	0	4	0	0	0	0	0	0	0	1
Urination h)	0	1	0	1	0	0	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-149 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	8	2	3	0	1	2	6	2	5	1	0
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	2	0	1	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-150 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	U	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	0	3	3	1	2	1	2	0	2	1	1
Defecation count	0	3	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-151 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	3	5	3	2	5	1	3	3	3	4	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	1
Urination h)	0	1	0	0	0	0	0	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-152 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	U	U	0	0	U	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	5	2	3	2	3	0	0	2	5	0	2
Defecation count	0	0	0	0	1	0	4	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-153 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	4	1	5	0	1	0	4	3	4	0	1
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	2	1	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-154 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	U	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	0	4	0	2	0	0	6	3	2	4	1
Defecation count	0	1	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-155 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	6	2	4	5	1	1	4	3	4	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-156 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	U	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	1	4	0	0	1	4	0	2	3	5	2	2
Defecation count	0	0	0	2	0	0	0	0	0	0	0	0
Urination h)	0	0	0	2	0	0	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-157 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	4	3	3	0	3	3	4	2	3	3	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	1	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-158 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	0	5	2	2	4	2	1	2	2	2	6
Defecation count	0	1	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-159 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	2	3	5	2	4	1	3	4	1	3	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	1	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-160 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	2	4	5	3	5	0	1	4	7	1	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	0	1	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-161 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	U	U	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	4	4	4	0	0	3	3	4	5	5	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-162 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	U	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	0	4	3	6	3	3	1	3	2	5	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	1	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-163 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	5	4	4	3	6	4	5	4	3	7	3
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-164 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	4	1	6	5	5	1	6	5	5	2	5
Defecation count	0	0	0	0	0	0	1	0	0	0	0	0
Urination h)	0	0	0	1	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-165 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1001-1012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	U	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	7	4	3	0	1	5	5	4	5	2	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-166 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2001-2012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	3	1	4	2	3	2	6	1	3	1	2	2
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-167 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3001-3012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	2	2	2	3	6	1	4	7	6	5	5
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	0	0	0	0	1	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-168 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4001-4012)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	1	1	3	3	7	1	4	3	5	2	7
Defecation count	0	0	0	0	0	0	0	0	1	0	0	0
Urination h)	1	0	1	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-169 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	4	6	7	5	10	7	7	12	8	6	9
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-170 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	9	7	9	3	6	7	3	12	8	8	2	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-171 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	7	8	7	9	2	6	3	3	6	6	8
Defecation count	0	0	0	0	1	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-172 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	9	6	5	9	6	9	3	6	8	5	8	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-173 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	5	7	4	9	11	12	4	10	4	7	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-174 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	10	9	6	5	5	7	8	10	9	10	6	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-175 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	7	5	12	8	6	11	9	1	7	6	9
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-176 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	10	6	6	6	2	4	5	6	9	1	9	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-177 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	4	3	7	4	8	11	12	7	8	5	11	4
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-178 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Arousal a)	0	0	0	0	0	0	0	0			0	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	
Stereotypy d)	0	0	0	0	0	0	0	0			0	
Gait e)	0	0	0	0	0	0	0	0			0	
Posture f)	N	N	N	N	N	N	N	N			N	
Grooming g)	0	0	0	0	0	0	0	0			0	
Rearing	5	6	9	4	4	6	6	11			6	
Defecation count	0	0	0	0	0	0	0	0			0	
Urination h)	0	0	0	1	0	0	0	0			0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NC: Not copulated
NP: Non-pregnant

Appendix 2-179 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	8	5	4	6	6	5	8	7	2		5	6
Defecation count	0	0	0	0	0	0	0	0	0		0	0
Urination h)	0	1	0	0	0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NP: Non-pregnant

Appendix 2-180 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 1)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	15	7	5	6	5	5	6	6	4	4	10	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-181 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	4	10	6	7	8	10	5	7	5	10	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-182 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Arousal a)	0	0	0	0	0	0	0	0			0	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	
Stereotypy d)	0	0	0	0	0	0	0	0			0	
Gait e)	0	0	0	0	0	0	0	0			0	
Posture f)	N	N	N	N	N	N	N	N			N	
Grooming g)	0	0	0	0	0	0	0	0			0	
Rearing	12	10	6	4	6	6	4	8			5	
Defecation count	0	0	0	0	0	0	0	0			0	
Urination h)	0	0	0	0	0	0	0	0			0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NC: Not copulated
NP: Non-pregnant

Appendix 2-183 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	7	6	3	6	6	6	5	4	6		9	6
Defecation count	0	0	0	0	0	0	0	0	0		0	0
Urination h)	1	0	0	0	0	0	0	0	1		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NP: Non-pregnant

Appendix 2-184 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 7)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	14	7	6	7	6	8	5	6	2	5	7	9
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-185 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	6	5	9	3	8	6	12	6	10	3	10	8
Defecation count	0	0	0	0	0	0	0	0	0	1	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-186 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Arousal a)	0	0	0	0	0	0	0	0			0	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	
Stereotypy d)	0	0	0	0	0	0	0	0			0	
Gait e)	0	0	0	0	0	0	0	0			0	
Posture f)	N	N	N	N	N	N	N	N			N	
Grooming g)	0	0	0	0	0	0	0	0			0	
Rearing	19	7	6	5	4	10	6	5			8	
Defecation count	0	0	0	0	0	0	0	0			0	
Urination h)	0	0	0	0	0	0	0	0			0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NC: Not copulated
NP: Non-pregnant

Appendix 2-187 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	9	4	6	6	6	5	8	4	5		6	6
Defecation count	0	0	0	0	0	0	0	0	0		0	0
Urination h)	0	0	0	0	0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NP: Non-pregnant

Appendix 2-188 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 14)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	8	9	3	5	4	10	5	4	5	5	6	8
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-189 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	2	5	5	6	4	5	7	5	6	4	8	7
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	1	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-190 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Arousal a)	0	0	0	0	0	0	0	0			0	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	
Stereotypy d)	0	0	0	0	0	0	0	0			0	
Gait e)	0	0	0	0	0	0	0	0			0	
Posture f)	N	N	N	N	N	N	N	N			N	
Grooming g)	0	0	0	0	0	0	0	0			0	
Rearing	8	5	4	5	4	7	4	3			6	
Defecation count	0	0	0	0	0	0	0	0			0	
Urination h)	0	0	0	0	0	0	0	0			0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NC: Not copulated
NP: Non-pregnant

Appendix 2-191 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	4	3	5	7	6	4	4	5	3		7	9
Defecation count	0	0	0	0	0	0	0	0	0		0	0
Urination h)	0	0	0	0	0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NP: Non-pregnant

Appendix 2-192 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Gestation day 20)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	13	5	6	6	1	7	2	5	4	6	4	6
Defecation count	0	0	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-193 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1101-1112)											
	1	2	3	4	5	6	7 i)	8	9	10	11	12
Arousal a)	0	0	0	0	0	0		0	0	0	0	0
Convulsion b)	0	0	0	0	0	0		0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0		0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0		0	0	0	0	0
Gait e)	0	0	0	0	0	0		0	0	0	0	0
Posture f)	N	N	N	N	N	N		N	N	N	N	N
Grooming g)	0	0	0	0	0	0		0	0	0	0	0
Rearing	5	7	10	5	6	7		6	9	4	13	10
Defecation count	0	0	0	0	0	0		0	0	0	0	0
Urination h)	0	0	0	0	0	0		0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
i) Necropsied on lactation day 0 because all pups were stillborn

Appendix 2-194 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 40

Parameter	Animal number (2101-2112)											
	1	2	3	4	5	6	7	8	9 NP	10 NP	11	12 NC
Arousal a)	0	0	0	0	0	0	0	0			0	
Convulsion b)	0	0	0	0	0	0	0	0			0	
Abnormal behavior c)	0	0	0	0	0	0	0	0			0	
Stereotypy d)	0	0	0	0	0	0	0	0			0	
Gait e)	0	0	0	0	0	0	0	0			0	
Posture f)	N	N	N	N	N	N	N	N			N	
Grooming g)	0	0	0	0	0	0	0	0			0	
Rearing	13	7	7	7	9	8	6	8			7	
Defecation count	0	0	0	0	0	0	0	0			0	
Urination h)	0	0	0	0	0	0	0	0			0	

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NC: Not copulated
NP: Non-pregnant

Appendix 2-195 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 200

Parameter	Animal number (3101-3112)											
	1	2	3	4	5	6	7	8	9	10 NP	11	12
Arousal a)	0	0	0	0	0	0	0	0	0		0	0
Convulsion b)	0	0	0	0	0	0	0	0	0		0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0		0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0		0	0
Gait e)	0	0	0	0	0	0	0	0	0		0	0
Posture f)	N	N	N	N	N	N	N	N	N		N	N
Grooming g)	0	0	0	0	0	0	0	0	0		0	0
Rearing	6	6	6	6	9	5	5	7	6		10	4
Defecation count	0	0	0	0	2	0	0	0	0		0	0
Urination h)	0	0	0	0	0	0	0	0	0		0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount
NP: Non-pregnant

Appendix 2-196 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Main group, Lactation day 4)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4112)											
	1	2	3	4	5	6	7	8	9	10	11	12
Arousal a)	0	0	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0	0	0
Rearing	5	5	10	5	9	8	6	8	5	4	6	10
Defecation count	0	0	0	0	1	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-197 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	7	7	9	5	6	3	2	8	5	8
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-198 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 1 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	7	4	3	8	6	5	5	9	3	4
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-199 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	4	8	8	7	6	5	5	10	5	4
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-200 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 2 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	9	5	5	5	6	11	9	7	3	3
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-201 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	6	9	12	4	5	5	6	8	7	11
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	1	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-202 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 3 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	9	6	5	10	5	11	8	8	4	6
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-203 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	5	9	9	6	6	4	5	11	9	9
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-204 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 4 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	5	9	6	8	5	10	9	6	5	5
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	1	0	0	0	0	0	1	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-205 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	4	10	14	6	6	6	5	13	9	9
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	1	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-206 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 5 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	7	8	9	7	8	11	12	12	5	8
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	1	0	1	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-207 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1113-1122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	7	10	14	6	7	7	5	8	8	6
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	0	0	0	0	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-208 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4113-4122)									
	13	14	15	16	17	18	19	20	21	22
Arousal a)	0	0	0	0	0	0	0	0	0	0
Convulsion b)	0	0	0	0	0	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0	0	0	0	0	0
Stereotypy d)	0	0	0	0	0	0	0	0	0	0
Gait e)	0	0	0	0	0	0	0	0	0	0
Posture f)	N	N	N	N	N	N	N	N	N	N
Grooming g)	0	0	0	0	0	0	0	0	0	0
Rearing	8	6	9	18	8	10	13	12	6	8
Defecation count	0	0	0	0	0	0	0	0	0	0
Urination h)	1	0	0	1	0	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-209 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	3	3	2	3
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	1

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-210 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	5	6	4	2	6
Defecation count	0	0	0	0	0
Urination h)	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-211 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	3	2	3	1	2
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-212 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in male rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	0	6	1	2	1
Defecation count	0	2	0	0	0
Urination h)	0	1	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-213 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	7	5	9	5	11
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-214 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 1 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	9	9	9	3	5
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-215 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	4	4	3	5	7
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-216 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual detailed clinical signs in female rats: open field observation
(Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Arousal a)	0	0	0	0	0
Convulsion b)	0	0	0	0	0
Abnormal behavior c)	0	0	0	0	0
Stereotypy d)	0	0	0	0	0
Gait e)	0	0	0	0	0
Posture f)	N	N	N	N	N
Grooming g)	0	0	0	0	0
Rearing	8	7	8	0	1
Defecation count	0	0	0	0	0
Urination h)	0	0	0	0	0

a) -2: Unconscious/semi-conscious, -1: Reduced awareness, 0: Normal, 1: Increased alertness, 2: Markedly alert
b) 0: None, 1: Minor, 2: Moderate, 3: Severe
c) 0: None, 1: Minor, 2: Moderate, 3: Severe
d) 0: None, 1: Minor, 2: Moderate, 3: Severe
e) U: No/minimal location, 0: Normal, 1: Slight, 2: Moderate, 3: Markedly
f) N: Normal, F: Flattened, H: Hunched
g) 0: None, 1: Occasional bouts (up to four), 2: Numerous bouts (more than four)
h) 0: None, 1: Small amount, 2: Moderate amount, 3: Large/excessive amount

Appendix 2-217 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	83	48	68	78	47

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-218 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 40

Parameter	Animal number (2008-2012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	51	60	55	69	43

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-219 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 200

Parameter	Animal number (3008-3012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	64	50	57	75	61

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-220 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	113	40	75	59	39

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-221 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Parameter	Animal number (1102-1112)				
	2	4	5	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	62	41	75	39	71

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-222 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 40

Parameter	Animal number (2101-2108)				
	1	2	4	5	8
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	57	48	43	64	65

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-223 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 200

Parameter	Animal number (3102-3109)				
	2	4	5	6	9
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	81	43	49	68	87

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-224 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Main group, Lactation day 4)
Dose (mg/kg): 1000

Parameter	Animal number (4101-4108)				
	1	4	5	7	8
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	58	50	91	70	53

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-225 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	80	73	40	55	65

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-226 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	52	65	42	53	88

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-227 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1008-1012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	53	39	59	62	46

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-228 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4008-4012)				
	8	9	10	11	12
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	100	72	92	48	58

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-229 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Parameter	Animal number (1118-1122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	63	69	61	68	63

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-230 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual manipulative test of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Parameter	Animal number (4118-4122)				
	18	19	20	21	22
Auditory response a)	0	0	0	0	0
Approach response b)	0	0	0	0	0
Touch response c)	0	0	0	0	0
Tail pinch response d)	0	0	0	0	0
Pupillary reflex e)	P	P	P	P	P
Aerial righting reflex (Total score)	0	0	0	0	0
Landing foot splay (mm)	35	83	45	42	76

a) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
b) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
c) -1: No reaction/ignores, 0: Normal, 1: Abnormality fearful/aggressive reaction
d) -2: None, -1: Weak, 0: Normal, 1: Exaggerate
e) P: Pass, both, F: Failed, neither, L: Left pupil responds, R: Right pupil responds

Appendix 2-231 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1008	1441	932
1009	1658	686
1010	1393	676
1011	1858	1019
1012	1593	705
Mean	1589	804
S.D.	185	160

Appendix 2-232 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 40

Animal number	Fore limb g	Hind limb g
2008	1554	668
2009	1430	665
2010	1495	687
2011	1684	848
2012	1624	696
Mean	1557	713
S.D.	101	77

Appendix 2-233 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 200

Animal number	Fore limb g	Hind limb g
3008	1647	864
3009	1373	741
3010	1572	739
3011	1517	625
3012	1320	628
Mean	1486	719
S.D.	137	99

Appendix 2-234 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Fore limb g	Hind limb g
4008	1381	1004
4009	1650	718
4010	1599	737
4011	1626	765
4012	1711	804
Mean	1593	806
S.D.	126	116

Appendix 2-235 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1102	995	632
1104	1427	837
1105	874	540
1111	1274	824
1112	1167	510
Mean	1147	669
S.D.	219	155

Appendix 2-236 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 40

Animal number	Fore limb g	Hind limb g
2101	1379	780
2102	1408	746
2104	1327	664
2105	1262	763
2108	1224	729
Mean	1320	736
S.D.	77	45

Appendix 2-237 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 200

Animal number	Fore limb g	Hind limb g
3102	1397	618
3104	1490	770
3105	1485	833
3106	1110	533
3109	1374	725
Mean	1371	696
S.D.	155	120

Appendix 2-238 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Main group, Lactation day 4)
Dose (mg/kg): 1000

Animal number	Fore limb g	Hind limb g
4101	1120	716
4104	1496	697
4105	1510	660
4107	1272	666
4108	1364	758
Mean	1352	699
S.D.	163	40

Appendix 2-239 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1118	1346	597
1119	1236	535
1120	1172	718
1121	1169	585
1122	1167	584
Mean	1218	604
S.D.	77	68

Appendix 2-240 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Fore limb g	Hind limb g
4118	1203	551
4119	1037	570
4120	1185	627
4121	1166	614
4122	1154	615
Mean	1149	595
S.D.	65	33

Appendix 2-241 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1008	1658	874
1009	1775	961
1010	1580	763
1011	1956	1048
1012	1484	805
Mean	1691	890
S.D.	183	116

Appendix 2-242 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Fore limb g	Hind limb g
4008	1946	1089
4009	1816	813
4010	1762	884
4011	1811	851
4012	1604	778
Mean	1788	883
S.D.	123	122

Appendix 2-243 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Fore limb g	Hind limb g
1118	1407	633
1119	1357	712
1120	1364	827
1121	1389	806
1122	1356	769
Mean	1375	749
S.D.	23	78

Appendix 2-244 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual grip strength of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Fore limb g	Hind limb g
4118	1321	837
4119	1289	836
4120	1458	657
4121	1290	598
4122	1359	701
Mean	1343	726
S.D.	70	107

Appendix 2-245 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1008	378	224	59	1	228	281	1171
1009	398	146	182	24	192	12	954
1010	423	320	305	40	83	215	1386
1011	392	412	360	252	105	6	1527
1012	447	402	190	29	35	68	1171
Mean	408	301	219	69	129	116	1242
S.D.	27	115	117	103	80	125	221

Unit: Count

Appendix 2-246 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 40

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
2008	323	257	72	13	30	53	748
2009	399	363	313	351	380	153	1959
2010	366	335	281	56	4	33	1075
2011	359	320	211	3	39	28	960
2012	392	261	40	11	4	19	727
Mean	368	307	183	87	91	57	1094
S.D.	30	47	123	149	162	55	505

Unit: Count

Appendix 2-247 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 200

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
3008	393	361	72	15	282	334	1457
3009	426	273	171	149	43	163	1225
3010	360	359	198	131	11	277	1336
3011	417	275	55	22	5	13	787
3012	280	208	149	9	63	15	724
Mean	375	295	129	65	81	160	1106
S.D.	59	65	63	69	115	147	331

Unit: Count

Appendix 2-248 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4008	351	111	0	5	45	10	522
4009	224	154	73	0	40	3	494
4010	440	390	326	149	80	43	1428
4011	293	293	70	58	65	0	779
4012	403	370	143	154	18	261	1349
Mean	342	264	122	73	50	63	914
S.D.	86	126	125	75	24	112	448

Unit: Count

Appendix 2-249 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1102	390	276	100	120	164	102	1152
1104	170	129	39	12	18	15	383
1105	389	229	298	16	8	28	968
1111	397	112	221	6	19	66	821
1112	206	89	6	8	4	15	328
Mean	310	167	133	32	43	45	730
S.D.	113	81	124	49	68	38	362

Unit: Count

Appendix 2-250 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 40

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
2101	225	337	278	212	200	178	1430
2102	255	28	12	34	16	9	354
2104	197	9	13	35	38	11	303
2105	253	188	79	271	231	192	1214
2108	473	361	331	365	85	39	1654
Mean	281	185	143	183	114	86	991
S.D.	110	166	151	146	97	91	625

Unit: Count

Appendix 2-251 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 200

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
3102	283	213	57	188	71	23	835
3104	228	130	178	77	13	116	742
3105	304	123	22	21	11	11	492
3106	169	62	18	19	9	62	339
3109	284	174	146	75	256	254	1189
Mean	254	140	84	76	72	93	719
S.D.	55	57	73	69	106	99	328

Unit: Count

Appendix 2-252 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Main group, Lactation day 4)
Dose (mg/kg): 1000

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4101	299	218	52	40	73	32	714
4104	421	71	73	33	34	17	649
4105	234	37	11	81	1	10	374
4107	312	118	104	167	29	17	747
4108	432	398	291	283	232	251	1887
Mean	340	168	106	121	74	65	874
S.D.	85	145	109	105	92	104	585

Unit: Count

Appendix 2-253 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1118	385	378	202	60	4	1	1030
1119	416	218	4	122	61	6	827
1120	409	375	166	6	15	22	993
1121	413	461	87	23	239	254	1477
1122	453	400	72	3	13	8	949
Mean	415	366	106	43	66	58	1055
S.D.	24	90	79	50	99	110	248

Unit: Count

Appendix 2-254 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4118	298	58	2	105	162	23	648
4119	326	337	239	324	248	5	1479
4120	382	274	95	87	251	246	1335
4121	394	74	4	0	326	411	1209
4122	439	402	329	167	28	2	1367
Mean	368	229	134	137	203	137	1208
S.D.	56	156	146	121	114	184	327

Unit: Count

Appendix 2-255 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1008	290	267	217	261	143	254	1432
1009	366	135	20	109	99	16	745
1010	366	234	251	160	20	10	1041
1011	356	382	407	192	150	364	1851
1012	412	404	331	260	195	15	1617
Mean	358	284	245	196	121	132	1337
S.D.	44	111	146	66	66	166	444

Unit: Count

Appendix 2-256 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Interval (minutes)						
	0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4008	439	306	327	274	326	266	1938
4009	374	291	141	198	7	49	1060
4010	422	300	161	89	37	63	1072
4011	393	299	351	346	323	268	1980
4012	401	303	331	309	316	308	1968
Mean	406	300	262	243	202	191	1604
S.D.	25	6	102	102	165	124	491

Unit: Count

Appendix 2-257 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
1118	359	311	280	11	21	22	1004
1119	353	313	73	53	7	18	817
1120	357	337	320	106	0	0	1120
1121	355	361	307	212	55	19	1309
1122	371	326	107	3	150	327	1284
Mean	359	330	217	77	47	77	1107
S.D.	7	20	118	86	62	140	204

Unit: Count

Appendix 2-258 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual motor activity of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Interval (minutes) 0-10	10-20	20-30	30-40	40-50	50-60	Total(0-60)
4118	245	16	181	11	7	3	463
4119	301	271	251	300	301	288	1712
4120	413	371	288	143	7	56	1278
4121	350	159	3	8	2	123	645
4122	341	338	328	145	9	79	1240
Mean	330	231	210	121	65	110	1068
S.D.	62	145	128	120	132	109	508

Unit: Count

Appendix 3-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
1001	402	413	429	450	473	502	516	114
1002	454	476	506	519	532	544	558	104
1003	421	447	467	482	494	510	517	96
1004	416	440	460	477	494	507	515	99
1005	411	430	452	473	504	523	537	126
1006	450	468	493	483	502	526	540	90
1007	418	439	459	480	500	510	519	101
1008	410	433	455	463	476	494	498	88
1009	383	392	405	413	445	467	479	96
1010	390	410	437	446	467	492	499	109
1011	432	456	491	515	528	556	562	130
1012	394	415	432	453	476	484	487	93
Mean	415	435	457	471	491	510	519	104
S.D.	22	25	29	29	25	25	26	14

Unit: g

Appendix 3-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 40

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
2001	432	453	481	490	519	548	557	125
2002	415	413	429	436	458	479	491	76
2003	405	411	423	427	447	467	475	70
2004	390	402	410	414	435	453	463	73
2005	437	460	487	504	536	555	557	120
2006	389	408	430	456	467	494	502	113
2007	405	419	434	454	472	495	505	100
2008	390	410	425	438	461	470	470	80
2009	451	481	510	530	565	599	611	160
2010	415	447	445	474	491	506	517	102
2011	413	421	436	464	481	499	507	94
2012	425	443	465	491	517	531	540	115
Mean	414	431	448	465	487	508	516	102
S.D.	20	25	31	34	39	43	43	26

Unit: g

Appendix 3-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 200

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
3001	393	401	413	440	459	488	502	109
3002	409	430	447	481	489	513	524	115
3003	438	454	482	505	529	548	565	127
3004	394	403	418	435	444	463	473	79
3005	419	427	438	453	470	483	499	80
3006	465	477	494	505	527	541	551	86
3007	407	420	434	444	463	482	493	86
3008	409	422	432	450	466	482	488	79
3009	422	443	463	484	503	515	521	99
3010	430	449	471	484	492	511	509	79
3011	410	425	426	441	459	474	479	69
3012	386	398	417	418	435	446	433	47
Mean	415	429	445	462	478	496	503	88
S.D.	22	24	27	29	30	31	35	22

Unit: g

Appendix 3-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
4001	414	421	421	433	455	464	478	64
4002	430	443	468	476	498	511	530	100
4003	441	458	478	487	515	534	541	100
4004	412	421	442	449	467	484	501	89
4005	412	419	434	441	450	465	478	66
4006	392	423	450	470	490	505	510	118
4007	418	420	440	462	484	502	517	99
4008	418	446	457	464	493	510	518	100
4009	394	410	419	428	444	459	467	73
4010	452	431	484	514	543	573	588	136
4011	405	421	440	453	469	482	491	86
4012	386	398	409	419	437	442	450	64
Mean	415	426	445	458	479	494	506	91
S.D.	20	16	23	27	31	36	37	22

Unit: g

Appendix 3-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	Gain 1-15
1101	261	281	292	31
1102	261	266	283	22
1103	242	247	256	14
1104	238	252	264	26
1105	236	247	255	19
1106	278	277	299	21
1107	241	241	263	22
1108	283	298	302	19
1109	239	244	250	11
1110	266	277	275	9
1111	250	255	262	12
1112	244	260	264	20
Mean	253	262	272	19
S.D.	16	18	18	6

Unit: g

Appendix 3-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 40

Animal number	Day of administration 1	8	15	Gain 1-15
2101	292	303	312	20
2102	249	266	280	31
2103	265	272	272	7
2104	251	270	277	26
2105	239	244	253	14
2106	247	261	273	26
2107	255	269	271	16
2108	256	257	266	10
2109	236	245	251	15
2110	245	248	266	21
2111	230	248	253	23
2112	242	254	258	16
Mean	251	261	269	19
S.D.	16	17	17	7

Unit: g

Appendix 3-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 200

Animal number	Day of administration 1	8	15	Gain 1-15
3101	293	284	304	11
3102	239	241	253	14
3103	242	251	260	18
3104	253	258	268	15
3105	252	251	264	12
3106	238	244	256	18
3107	268	285	300	32
3108	255	260	273	18
3109	258	269	279	21
3110	264	274	279	15
3111	247	254	254	7
3112	270	283	280	10
Mean	257	263	273	16
S.D.	16	16	17	6

Unit: g

Appendix 3-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats during the pre-mating period (Main group)
Dose (mg/kg): 1000

Animal number	Day of administration 1	8	15	Gain 1-15
4101	236	238	254	18
4102	235	253	265	30
4103	266	282	288	22
4104	253	262	277	24
4105	271	269	281	10
4106	265	272	284	19
4107	251	255	269	18
4108	238	246	260	22
4109	259	273	283	24
4110	247	268	284	37
4111	232	249	265	33
4112	247	251	263	16
Mean	250	260	273	23
S.D.	13	13	11	8

Unit: g

Appendix 3-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 0	7	14	20a)	Gain 0-20
1101	301	336	365	445	144
1102	293	326	361	446	153
1103	254	292	325	397	143
1104	261	300	347	424	163
1105	256	289	331	395	139
1106	303	351	383	469	166
1107	267	298	320	334	67
1108	304	331	351	437	133
1109	261	306	352	445	184
1110	295	323	346	410	115
1111	268	300	330	416	148
1112	272	309	347	423	151
Mean	278	313	347	420	142
S.D.	20	20	18	35	29

Unit: g
a): Gestation day

Appendix 3-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 40

Dam number	Administration 0	7	14	20a)	Gain 0-20
2101	323	359	384	466	143
2102	280	320	357	434	154
2103	284	311	350	446	162
2104	273	326	360	427	154
2105	257	289	323	400	143
2106	289	312	340	421	132
2107	292	324	366	441	149
2108	272	327	364	462	190
2109	Non-pregnant				
2110	Non-pregnant				
2111	256	306	344	442	186
2112	Not copulated				
Mean	281	319	354	438	157
S.D.	20	19	18	20	20

Unit: g
a): Gestation day

Appendix 3-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 200

Dam number	Administration 0	7	14	20a)	Gain 0-20
3101	300	343	375	479	179
3102	256	313	359	439	183
3103	267	312	344	433	166
3104	285	324	369	448	163
3105	265	303	350	440	175
3106	255	295	332	424	169
3107	295	342	377	447	152
3108	273	318	351	441	168
3109	279	317	342	422	143
3110	Non-pregnant				
3111	272	306	343	403	131
3112	297	342	377	476	179
Mean	277	320	356	441	164
S.D.	16	17	16	22	16

Unit: g
a): Gestation day

Appendix 3-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the gestation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration 0	7	14	20a)	Gain 0-20
4101	262	296	335	428	166
4102	271	304	332	424	153
4103	293	334	371	464	171
4104	279	321	359	447	168
4105	289	335	377	472	183
4106	288	320	352	444	156
4107	273	304	350	438	165
4108	274	307	350	432	158
4109	287	324	365	468	181
4110	272	320	366	447	175
4111	273	309	339	426	153
4112	279	308	346	440	161
Mean	278	315	354	444	166
S.D.	9	12	14	16	10

Unit: g
a): Gestation day

Appendix 3-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 0	4a)	Gain 0-4
1101	338	363	25
1102	367	371	4
1103	315	337	22
1104	337	368	31
1105	332	336	4
1106	392	385	-7
1107b)			
1108	337	358	21
1109	315	341	26
1110	337	345	8
1111	292	352	60
1112	343	337	-6
Mean	337	354	17
S.D.	26	16	19

Unit: g
a): Lactation day
b): Necropsied on lactation day 0 because all pups were stillborn

Appendix 3-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 40

Dam number	Administration 0	Administration 4a)	Gain 0-4
2101	371	387	16
2102	315	370	55
2103	300	353	53
2104	340	357	17
2105	322	334	12
2106	329	329	0
2107	361	363	2
2108	385	361	-24
2109	Non-pregnant		
2110	Non-pregnant		
2111	326	333	7
2112	Not copulated		
Mean	339	354	15
S.D.	28	19	25

Unit: g
a): Lactation day

Appendix 3-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 200

Dam number	Administration 0	Administration 4a)	Gain 0-4
3101	347	405	58
3102	354	349	-5
3103	332	374	42
3104	355	369	14
3105	367	379	12
3106	334	354	20
3107	351	382	31
3108	317	343	26
3109	298	350	52
3110	Non-pregnant		
3111	323	338	15
3112	374	358	-16
Mean	341	364	23
S.D.	23	20	23

Unit: g
a): Lactation day

Appendix 3-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of dams during the lactation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration 0	Administration 4a)	Gain 0-4
4101	307	348	41
4102	330	334	4
4103	367	373	6
4104	359	359	0
4105	342	392	50
4106	318	372	54
4107	339	374	35
4108	352	376	24
4109	335	368	33
4110	359	347	-12
4111	317	348	31
4112	327	354	27
Mean	338	362	24
S.D.	19	16	21

Unit: g
a): Lactation day

Appendix 3-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
1113	257	261	282	294	302	304	315	58
1114	264	268	282	291	291	312	315	51
1115	243	253	254	247	257	272	266	23
1116	256	271	285	292	294	304	309	53
1117	252	267	263	280	288	295	295	43
1118	273	273	286	286	295	296	307	34
1119	240	258	263	280	290	291	296	56
1120	256	278	291	300	297	321	320	64
1121	232	253	256	257	275	281	284	52
1122	232	254	262	265	284	289	285	53
Mean	251	264	272	279	287	297	299	49
S.D.	14	9	14	17	13	14	17	12

Unit: g

Appendix 3-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats (Satellite group, Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration 1	8	15	22	29	36	42	Gain 1-42
4113	282	298	324	316	323	337	339	57
4114	259	262	271	286	293	301	306	47
4115	245	250	254	275	291	291	299	54
4116	236	253	259	270	281	286	290	54
4117	244	258	272	277	287	289	298	54
4118	244	253	263	259	275	278	280	36
4119	253	265	273	282	278	284	288	35
4120	254	266	280	280	291	306	300	46
4121	248	256	254	268	277	299	306	58
4122	286	294	309	326	330	337	343	57
Mean	255	266	276	284	293	301	305	50
S.D.	17	17	23	21	19	21	21	9

Unit: g

Appendix 3-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14	Gain 1-14
1008	502	506	521	19
1009	482	497	501	19
1010	498	519	523	25
1011	563	580	584	21
1012	491	502	511	20
Mean	507	521	528	21
S.D.	32	34	33	2

Unit: g

Appendix 3-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of male rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery 1	8	14	Gain 1-14
4008	521	540	555	34
4009	467	486	500	33
4010	593	622	635	42
4011	488	500	505	17
4012	451	463	475	24
Mean	504	522	534	30
S.D.	56	62	63	10

Unit: g

Appendix 3-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14	Gain 1-14
1118	311	321	313	2
1119	287	305	301	14
1120	321	325	328	7
1121	281	292	294	13
1122	286	296	304	18
Mean	297	308	308	11
S.D.	18	15	13	6

Unit: g

Appendix 3-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of female rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery 1	8	14	Gain 1-14
4118	281	282	287	6
4119	294	291	289	-5
4120	304	309	308	4
4121	312	314	316	4
4122	340	343	339	-1
Mean	306	308	308	2
S.D.	22	24	21	5

Unit: g

Appendix 4-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 0

Animal number	Day of administration					
	2	8	15	30	36	42
1001	26	25	26	27	28	28
1002	33	31	32	29	29	32
1003	31	30	29	29	29	27
1004	28	28	26	28	26	28
1005	29	27	30	28	29	30
1006	33	33	31	31	29	31
1007	26	29	28	28	26	30
1008	28	26	28	27	25	28
1009	25	23	25	26	27	27
1010	27	29	29	27	29	28
1011	33	27	34	32	35	31
1012	32	29	24	24	26	26
Mean	29	28	29	28	28	29
S.D.	3	3	3	2	3	2

Unit: g/rat/day

Appendix 4-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 40

Animal number	Day of administration					
	2	8	15	30	36	42
2001	32	30	32	30	27	30
2002	23	24	27	27	28	29
2003	27	25	25	24	29	28
2004	26	26	27	25	27	28
2005	28	26	29	25	31	26
2006	26	24	28	30	31	27
2007	27	23	25	26	29	27
2008	29	28	28	24	31	30
2009	32	33	35	33	36	35
2010	30	28	26	31	28	28
2011	28	28	27	28	30	35
2012	29	28	28	30	29	32
Mean	28	27	28	28	30	30
S.D.	3	3	3	3	2	3

Unit: g/rat/day

Appendix 4-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 200

Animal number	Day of administration					
	2	8	15	30	36	42
3001	25	22	25	27	29	29
3002	35	28	30	31	38	39
3003	30	28	27	29	30	33
3004	25	26	28	28	27	29
3005	26	25	24	26	25	28
3006	32	30	28	28	30	32
3007	26	25	27	30	29	32
3008	27	26	25	24	29	26
3009	28	22	28	26	29	29
3010	29	25	28	26	28	26
3011	26	26	23	26	26	26
3012	26	24	29	29	29	24
Mean	28	26	27	28	29	29
S.D.	3	2	2	2	3	4

Unit: g/rat/day

Appendix 4-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration					
	2	8	15	30	36	42
4001	27	26	25	29	28	26
4002	32	25	27	32	28	34
4003	27	28	30	29	32	32
4004	31	27	29	28	28	33
4005	24	23	26	25	23	26
4006	29	30	32	33	29	31
4007	24	23	30	29	29	32
4008	30	29	28	26	25	26
4009	23	26	28	22	28	26
4010	32	0	32	34	32	35
4011	25	28	27	27	25	27
4012	24	27	28	26	26	28
Mean	27	24	29	28	28	30
S.D.	3	8	2	3	3	3

Unit: g/rat/day

Appendix 4-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	Day of administration 2	8	15
1101	13	26	23
1102	25	19	24
1103	17	20	21
1104	22	20	22
1105	21	20	17
1106	20	17	26
1107	22	18	22
1108	18	29	22
1109	17	17	14
1110	21	23	15
1111	24	18	21
1112	23	23	24
Mean	20	21	21
S.D.	3	4	4

Unit: g/rat/day

Appendix 4-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 40

Animal number	Day of administration 2	8	15
2101	24	24	26
2102	19	22	24
2103	18	20	14
2104	22	21	23
2105	23	14	23
2106	26	25	23
2107	19	22	16
2108	23	15	21
2109	15	23	22
2110	24	18	22
2111	20	21	21
2112	16	19	18
Mean	21	20	21
S.D.	3	3	3

Unit: g/rat/day

Appendix 4-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 200

Animal number	Day of administration 2	8	15
3101	26	17	26
3102	21	13	21
3103	20	18	19
3104	22	17	22
3105	22	15	20
3106	20	16	20
3107	19	20	24
3108	22	18	26
3109	25	20	21
3110	18	22	22
3111	22	21	18
3112	26	24	20
Mean	22	18	22
S.D.	3	3	3

Unit: g/rat/day

Appendix 4-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats during the pre-mating period (Main group)
Dose (mg/kg): 1000

Animal number	Day of administration 2	8	15
4101	22	18	21
4102	23	22	20
4103	27	28	22
4104	21	19	21
4105	23	17	22
4106	19	21	24
4107	20	17	18
4108	23	20	22
4109	23	24	25
4110	25	22	26
4111	18	21	24
4112	19	20	22
Mean	22	21	22
S.D.	3	3	2

Unit: g/rat/day

Appendix 4-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 0

Dam number	Administration			
	1	7	14	20a)
1101	25	26	26	26
1102	24	24	25	27
1103	26	27	21	22
1104	23	27	30	27
1105	21	22	23	20
1106	27	35	34	31
1107	21	26	24	21
1108	29	28	25	26
1109	21	29	28	30
1110	23	28	27	23
1111	22	23	25	27
1112	25	24	28	24
Mean	24	27	26	25
S.D.	3	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 4-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 40

Dam number	Administration			
	1	7	14	20a)
2101	26	27	27	27
2102	19	28	29	25
2103	20	23	26	25
2104	27	28	31	25
2105	24	24	25	22
2106	21	24	28	26
2107	25	30	34	24
2108	27	34	32	25
2109	Non-pregnant			
2110	Non-pregnant			
2111	14	31	30	28
2112	Not copulated			
Mean	23	28	29	25
S.D.	4	4	3	2

Unit: g/rat/day
a): Gestation day

Appendix 4-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 200

Dam number	Administration 1	7	14	20a)
3101	26	30	30	32
3102	22	28	29	28
3103	21	25	23	23
3104	23	28	27	26
3105	22	24	28	23
3106	22	24	23	23
3107	24	27	29	26
3108	24	29	28	26
3109	25	27	22	20
3110	Non-pregnant			
3111	21	31	30	21
3112	29	32	33	26
Mean	24	28	27	25
S.D.	2	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 4-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the gestation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration			
	1	7	14	20a)
4101	27	28	26	22
4102	24	25	26	27
4103	21	34	29	29
4104	27	27	27	25
4105	28	33	34	24
4106	22	26	25	27
4107	24	22	25	24
4108	28	27	27	26
4109	20	29	29	29
4110	26	27	30	31
4111	23	25	23	24
4112	21	24	28	28
Mean	24	27	27	26
S.D.	3	3	3	3

Unit: g/rat/day
a): Gestation day

Appendix 4-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 0

Dam number	Administration 2	4a)
1101	33	47
1102	24	47
1103	30	35
1104	35	46
1105	21	36
1106	27	51
1107b)		
1108	33	45
1109	35	46
1110	26	40
1111	43	54
1112	112	44
Mean	38	45
S.D.	25	6

Unit: g/rat/day
a): Lactation day
b): Necropsied on lactation day 0 because all pups were stillborn

Appendix 4-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 40

Dam number	Administration	
	2	4a)
2101	33	53
2102	38	54
2103	42	47
2104	20	37
2105	28	50
2106	20	46
2107	26	45
2108	22	45
2109	Non-pregnant	
2110	Non-pregnant	
2111	17	47
2112	Not copulated	
Mean	27	47
S.D.	9	5

Unit: g/rat/day
a): Lactation day

Appendix 4-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 200

Dam number	Administration	
	2	4a)
3101	45	54
3102	30	42
3103	39	50
3104	27	55
3105	33	46
3106	19	51
3107	32	41
3108	30	48
3109	37	55
3110	Non-pregnant	
3111	27	44
3112	26	47
Mean	31	48
S.D.	7	5

Unit: g/rat/day
a): Lactation day

Appendix 4-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of dams during the lactation period (Main group)
Dose (mg/kg): 1000

Dam number	Administration	
	2	4a)
4101	36	54
4102	37	48
4103	33	45
4104	30	48
4105	42	52
4106	40	60
4107	38	52
4108	37	49
4109	46	47
4110	27	44
4111	39	47
4112	39	57
Mean	37	50
S.D.	5	5

Unit: g/rat/day
a): Lactation day

Appendix 4-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats (Satellite group, Administration period)
Dose (mg/kg): 0

Animal number	Day of administration					
	2	8	15	30	36	42
1113	20	16	21	25	18	26
1114	19	22	22	20	26	26
1115	16	23	21	14	22	16
1116	21	23	20	22	20	24
1117	20	22	17	19	21	22
1118	21	18	21	20	18	21
1119	22	23	17	21	19	21
1120	23	24	22	23	25	25
1121	20	19	20	14	21	21
1122	19	20	20	17	23	19
Mean	20	21	20	20	21	22
S.D.	2	3	2	4	3	3

Unit: g/rat/day

Appendix 4-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats (Satellite group, Administration period)
Dose (mg/kg): 1000

Animal number	Day of administration					
	2	8	15	30	36	42
4113	20	20	24	18	22	23
4114	20	19	18	22	22	23
4115	18	20	17	24	20	24
4116	19	23	16	23	19	20
4117	20	14	24	21	18	23
4118	12	20	22	13	21	17
4119	20	19	24	22	15	19
4120	19	20	21	22	22	18
4121	17	19	20	25	25	25
4122	18	23	22	15	18	23
Mean	18	20	21	21	20	22
S.D.	2	2	3	4	3	3

Unit: g/rat/day

Appendix 4-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14
1008	27	25	29
1009	28	30	27
1010	27	31	29
1011	31	35	31
1012	27	29	25
Mean	28	30	28
S.D.	2	4	2

Unit: g/rat/day

Appendix 4-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of male rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery 1	8	14
4008	35	32	31
4009	28	27	29
4010	33	36	37
4011	24	26	25
4012	30	29	27
Mean	30	30	30
S.D.	4	4	5

Unit: g/rat/day

Appendix 4-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats (Recovery period)
Dose (mg/kg): 0

Animal number	Day of recovery 1	8	14
1118	21	26	16
1119	15	23	20
1120	22	23	27
1121	17	23	22
1122	18	23	22
Mean	19	24	21
S.D.	3	1	4

Unit: g/rat/day

Appendix 4-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual food consumption of female rats (Recovery period)
Dose (mg/kg): 1000

Animal number	Day of recovery 1	8	14
4118	20	13	23
4119	21	19	17
4120	21	24	23
4121	23	26	24
4122	20	24	22
Mean	21	21	22
S.D.	1	5	3

Unit: g/rat/day

Appendix 5-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
1008	8.5	+	+-	-	+-	-	0.0*	+-	Y
1009	>=9.0	+-	+-	-	-	-	0.0*	+-	Y
1010	>=9.0	+	+	-	-	-	0.0*	+-	Y
1011	8.5	+-	+-	-	+-	-	0.0*	+-	Y
1012	7.5	+	+-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1008	-	-	+-	-	-	+-	-
1009	-	-	+-	-	-	+-	-
1010	-	-	+-	-	-	+-	-
1011	-	-	+-	-	-	+-	-
1012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1008	37	21.8	1630	2.27	5.64	2.62
1009	38	15.8	2518	1.86	6.69	2.81
1010	37	13.4	2200	1.58	4.62	2.01
1011	49	22.5	2212	2.57	7.65	3.47
1012	39	10.3	2204	1.22	3.53	1.57
Mean	40	16.8	2153	1.90	5.63	2.50
S.D.	5	5.3	322	0.54	1.63	0.73

Appendix 5-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 40

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
2008	8.5	+	+	-	-	-	0.0*	+-	Y
2009	8.0	+-	+	-	-	-	0.0*	+-	Y
2010	8.5	+	+-	-	-	-	0.0*	+-	Y
2011	8.5	+	+	-	-	-	0.0*	+-	Y
2012	>=9.0	+	+-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 40

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
2008	-	-	+-	-	-	+-	-
2009	-	-	+-	-	-	-	-
2010	-	-	+-	-	-	+-	-
2011	-	-	+-	-	-	+-	-
2012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 40

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
2008	42	19.9	1722	2.03	5.34	2.23
2009	57	32.6	1558	3.39	7.78	3.85
2010	65	31.2	1374	2.50	6.53	3.06
2011	48	22.9	1880	2.38	6.59	2.98
2012	40	15.1	2148	2.02	5.01	2.23
Mean	50	24.3	1736	2.46	6.25	2.87
S.D.	11	7.5	297	0.56	1.11	0.68

Appendix 5-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 200

Animal number	pH	1) Protein	2) Ketone body	3) Glucose	4) Occult blood	5) Bilirubin	T-BIL mg/dL	6) Urobilinogen	7) Color
3008	7.0	+	+-	-	-	-	0.0*	+-	Y
3009	>=9.0	+-	+-	-	-	-	0.0*	+-	Y
3010	>=9.0	++	+	-	-	-	0.0*	+-	Y
3011	>=9.0	+	+	-	-	-	0.0*	+-	Y
3012	8.5	+-	+-	-	+++	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 200

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
3008	-	-	+-	-	-	-	-
3009	-	-	+-	-	-	-	-
3010	-	-	+-	-	-	+-	-
3011	-	-	+-	-	-	+-	-
3012	+-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 200

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
3008	39	16.8	1586	2.18	3.82	1.92
3009	50	19.9	1810	2.51	5.49	2.23
3010	37	17.9	1860	2.83	4.93	2.51
3011	36	14.6	2062	2.34	4.30	2.16
3012	20	12.5	2006	3.08	2.87	2.08
Mean	36	16.3	1865	2.59	4.28	2.18
S.D.	11	2.9	187	0.37	1.01	0.22

Appendix 5-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
4008	8.0	+	+	-	-	+	0.0*	+-	LP
4009	7.5	+-	+-	-	-	+	0.0*	+-	LP
4010	8.0	+	+	+	-	+	0.0*	+-	LP
4011	8.0	++	+	-	-	++	0.0*	+-	LP
4012	8.0	++	+	-	+-	+++	0.0*	+-	LP

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4008	-	-	+-	-	-	+-	-
4009	-	-	+-	-	-	+-	-
4010	-	-	+-	-	-	+-	-
4011	-	-	+-	-	-	+-	-
4012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4008	57	19.1	2016	4.93	5.06	2.98
4009	31	13.3	2818	5.56	4.34	2.50
4010	60	18.1	2244	5.76	5.12	2.97
4011	47	17.6	2074	6.16	4.44	2.85
4012	40	13.3	2562	5.32	4.03	2.82
Mean	47	16.3	2343	5.55	4.60	2.82
S.D.	12	2.8	340	0.46	0.47	0.19

Appendix 5-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
1118	>=9.0	-	-	-	-	-	0.0*	+-	Y
1119	>=9.0	-	-	-	-	-	0.0*	+-	Y
1120	7.5	+-	-	-	-	-	0.0*	+-	Y
1121	8.5	-	-	-	-	-	0.0*	+-	Y
1122	8.0	-	-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1118	-	-	+-	-	-	+-	-
1119	-	-	+-	-	-	+-	-
1120	-	-	+-	-	-	+-	-
1121	-	-	+-	-	-	-	-
1122	-	-	+-	-	-	-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1118	36	13.3	1812	1.12	3.73	1.62
1119	26	12.6	2094	1.51	4.33	2.02
1120	31	6.8	2672	0.98	2.68	1.32
1121	23	5.5	3070	1.10	2.53	1.12
1122	33	10.3	2190	1.28	3.22	1.26
Mean	30	9.7	2368	1.20	3.30	1.47
S.D.	5	3.5	500	0.20	0.75	0.36

Appendix 5-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
4118	8.5	+	-	-	-	+	0.0*	+-	LP
4119	8.5	++	+-	+	+-	++	0.0*	+	LP
4120	7.0	++	+-	+	+-	+++	0.0*	+	LP
4121	7.5	++	-	-	++	-	0.0*	+-	LP
4122	7.5	+-	-	-	-	+	0.0*	+-	LP

1)	- : 0 mg/dL	+- : 15 mg/dL	+ : 30 mg/dL	++ : 100 mg/dL	+++ : >=300 mg/dL
2)	- : 0 mg/dL	+- : 5 mg/dL	+ : 15 mg/dL	++ : 40 mg/dL	+++ : 80 mg/dL
3)	- : 0 mg/dL	+ : 100 mg/dL	++ : 250 mg/dL	+++ : 500 mg/dL	++++ : >=1000 mg/dL
4)	- : 0 mg/dL	+- : 0.015 mg/dL	+ : 0.062 mg/dL	++ : 0.135 mg/dL	+++ : 0.405 mg/dL
5)	- : 0 mg/dL	+ : 0.8 mg/dL	++ : 1.6 mg/dL	+++ : 3.2 mg/dL	
6)	+- : 0.1-1.0 E.U./dL	+ : 2.0 E.U./dL	++ : 4.0 E.U./dL	+++ : >=8.0 E.U./dL	
7)	LY : Light yellow	Y : Yellow	DY : Dark yellow	LP : Light purple	B : Brown

*: Re-analyzed value

Appendix 5-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4118	-	-	+-	-	-	+-	-
4119	-	-	+-	-	-	+-	-
4120	-	-	+-	-	-	+-	-
4121	++	++	+-	-	-	-	-
4122	-	-	+-	-	-	-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of female rats (Satellite group, Week 6 of administration)
Dose (mg/kg): 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4118	24	10.1	2234	3.41	2.48	1.86
4119	24	7.7	2502	2.53	2.26	1.29
4120	33	8.1	3206	3.19	3.06	1.68
4121	63	23.2	1088	3.43	3.04	1.86
4122	51	19.7	1302	3.23	3.03	1.69
Mean	39	13.8	2066	3.16	2.77	1.68
S.D.	17	7.2	874	0.37	0.38	0.23

Appendix 5-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
1008	>=9.0	+-	+-	-	+++	-	0.0*	+-	Y
1009	>=9.0	+	+-	-	-	-	0.0*	+-	Y
1010	8.0	+	+	-	-	-	0.0*	+-	Y
1011	8.5	+-	+-	-	-	-	0.0*	+-	Y
1012	8.5	+	+-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1008	-	-	+-	-	-	-	-
1009	-	-	+-	-	-	+-	-
1010	-	-	+-	-	-	+-	-
1011	-	-	+-	-	-	+-	-
1012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1008	45	20.4	1846	1.80	6.12	2.53
1009	30	12.4	2306	1.22	4.65	1.98
1010	42	15.4	1906	1.82	4.50	2.13
1011	66	32.4	1724	2.40	8.41	3.56
1012	42	12.0	1894	0.98	3.81	1.63
Mean	45	18.5	1935	1.64	5.50	2.37
S.D.	13	8.5	219	0.56	1.83	0.74

Appendix 5-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
4008	>=9.0	+-	+-	-	-	-	0.0*	+-	Y
4009	>=9.0	+	+-	-	-	+	0.0*	+-	Y
4010	8.5	+	+-	-	+-	+	0.0*	+-	Y
4011	8.5	+	+-	-	+-	+	0.0*	+-	B
4012	8.5	++	+	-	-	++	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4008	-	-	+-	-	-	+-	-
4009	-	-	+-	-	-	+-	-
4010	-	-	+-	-	-	+-	-
4011	-	-	+-	-	-	+-	-
4012	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of male rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4008	44	20.8	1934	1.50	6.78	2.66
4009	32	16.0	2046	1.57	5.43	2.27
4010	50	21.2	1944	2.12	6.44	3.14
4011	36	16.7	2176	1.50	5.97	2.27
4012	32	12.0	2704	1.58	5.09	2.23
Mean	39	17.3	2161	1.65	5.94	2.51
S.D.	8	3.8	319	0.26	0.70	0.39

Appendix 5-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
1118	>=9.0	-	-	-	-	-	0.0*	+-	Y
1119	7.5	+-	-	-	-	+	0.0*	+-	Y
1120	8.5	-	-	-	-	-	0.0*	+-	Y
1121	7.0	+	-	-	-	-	0.0*	+-	Y
1122	7.5	-	-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
1118	-	-	+-	-	-	+-	-
1119	-	-	+-	-	-	+-	-
1120	-	-	+-	-	-	+-	-
1121	-	-	+-	-	-	+-	-
1122	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 0

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
1118	30	9.8	2196	1.29	3.39	1.47
1119	26	9.0	2386	1.21	3.07	1.42
1120	37	12.5	2160	1.28	4.42	1.65
1121	32	8.8	2614	0.88	3.67	1.44
1122	39	11.0	2196	1.03	3.73	1.45
Mean	33	10.2	2310	1.14	3.66	1.49
S.D.	5	1.5	191	0.18	0.50	0.09

Appendix 5-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	pH	1) Pro-tein	2) Ketone body	3) Glu-cose	4) Occult blood	5) Bili-rubin	T-BIL mg/dL	6) Urobi-linogen	7) Color
4118	7.0	+-	-	-	-	+	0.0*	+-	Y
4119	>=9.0	-	-	-	+-	-	0.0*	+-	Y
4120	7.0	++	+-	-	+-	++	0.0*	+-	Y
4121	8.5	++	-	-	-	-	0.0*	+-	Y
4122	8.0	-	-	-	-	-	0.0*	+-	Y

1) - : 0 mg/dL +- : 15 mg/dL + : 30 mg/dL ++ : 100 mg/dL +++ : >=300 mg/dL
2) - : 0 mg/dL +- : 5 mg/dL + : 15 mg/dL ++ : 40 mg/dL +++ : 80 mg/dL
3) - : 0 mg/dL + : 100 mg/dL ++ : 250 mg/dL +++ : 500 mg/dL ++++ : >=1000 mg/dL
4) - : 0 mg/dL +- : 0.015 mg/dL + : 0.062 mg/dL ++ : 0.135 mg/dL +++ : 0.405 mg/dL
5) - : 0 mg/dL + : 0.8 mg/dL ++ : 1.6 mg/dL +++ : 3.2 mg/dL
6) +- : 0.1-1.0 E.U./dL + : 2.0 E.U./dL ++ : 4.0 E.U./dL +++ : >=8.0 E.U./dL
7) LY : Light yellow Y : Yellow DY : Dark yellow LP : Light purple B : Brown
*: Re-analyzed value

Appendix 5-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	URINE SEDIMENT						
						CRYSTALLIZATION	
	RBC	WBC	SEC	SREC	Cast	PS	CO
4118	-	-	+-	-	-	+-	-
4119	-	-	+-	-	-	-	-
4120	-	-	+-	-	-	+-	-
4121	+++	+	+-	-	-	+-	-
4122	-	-	+-	-	-	+-	-

SEC : Squamous Epithelial Cell
SREC : Small Round Epithelial Cell
PS : Phosphate Salts
CO : Calcium Oxalate

\- : Negative
+- : Slight
\+ : Mild
++ : Moderate
+++ : Severe

Appendix 5-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual water intake and urinalysis of female rats (Week 2 of recovery)
Dose (mg/kg): 1000

Animal number	Water intake mL/24h	Urine volume mL/24h	Osmotic Pressure mOsm/kg	Na mmol/24h	K mmol/24h	Cl mmol/24h
4118	33	10.0	2390	1.14	3.76	1.52
4119	31	9.2	2534	1.05	3.54	1.20
4120	27	6.4	3146	0.90	2.90	1.20
4121	47	20.1	1204	1.37	3.78	1.77
4122	39	18.9	1792	1.63	5.25	2.19
Mean	35	12.9	2213	1.22	3.85	1.58
S.D.	8	6.2	742	0.29	0.86	0.42

Appendix 6-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1001	909	15.9	46.2	50.8	17.5	34.5	2.2	101.2	12.7	20.4	249
1002	933	16.5	47.3	50.6	17.7	34.9	1.7	110.2	16.5	19.0	306
1003	924	15.4	44.2	47.9	16.7	34.8	1.9	112.6	12.8	19.4	249
1004	899	16.2	46.1	51.3	18.0	35.1	1.9	113.9	14.1	17.7	225
1005	933	16.3	46.7	50.0	17.4	34.9	2.2	121.7	13.6	18.0	241
Mean	920	16.1	46.1	50.1	17.5	34.8	2.0	111.9	13.9	18.9	254
S.D.	15	0.4	1.2	1.3	0.5	0.2	0.2	7.4	1.5	1.1	31

Appendix 6-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1001	58.0	77.8	18.4	0.8	0.5	2.3	0.2	45.1	10.7	0.4	0.3	1.3	0.1
1002	59.9	74.8	18.9	1.1	0.5	4.2	0.4	44.8	11.3	0.7	0.3	2.5	0.2
1003	111.0	80.6	15.4	1.2	0.4	2.0	0.5	89.4	17.0	1.3	0.4	2.3	0.6
1004	59.6	70.1	26.2	1.6	0.3	1.6	0.2	41.8	15.6	0.9	0.2	1.0	0.1
1005	82.7	74.2	19.4	1.3	0.5	4.2	0.4	61.4	16.1	1.1	0.4	3.4	0.3
Mean	74.2	75.5	19.7	1.2	0.4	2.9	0.3	56.5	14.1	0.9	0.3	2.1	0.3
S.D.	22.9	4.0	4.0	0.3	0.1	1.2	0.1	19.9	2.9	0.3	0.1	1.0	0.2

LUC: Large unstained cells

Appendix 6-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 40

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
2001	866	15.6	45.2	52.2	18.1	34.6	2.5	94.6	12.2	17.3	253
2002	920	16.0	45.7	49.7	17.4	35.0	1.7	98.4	14.1	19.9	267
2003	958	16.5	47.3	49.4	17.2	34.8	1.6	95.3	15.2	17.9	239
2004	863	15.6	43.8	50.8	18.1	35.6	2.1	100.4	12.5	16.0	225
2005	886	16.2	45.5	51.3	18.2	35.6	1.9	99.2	12.4	17.4	271
Mean	899	16.0	45.5	50.7	17.8	35.1	2.0	97.6	13.3	17.7	251
S.D.	40	0.4	1.3	1.2	0.5	0.5	0.4	2.5	1.3	1.4	19

Appendix 6-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 40

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2001	85.4	72.6	22.9	1.1	0.5	2.7	0.2	62.0	19.5	0.9	0.4	2.3	0.2
2002	84.2	81.0	14.6	1.2	0.3	2.4	0.4	68.2	12.3	1.0	0.3	2.0	0.3
2003	90.8	74.3	22.1	1.5	0.3	1.7	0.2	67.5	20.1	1.3	0.3	1.6	0.2
2004	65.6	78.9	16.7	1.2	0.3	2.3	0.5	51.7	10.9	0.8	0.2	1.5	0.3
2005	71.0	72.2	23.0	0.9	0.5	3.2	0.3	51.3	16.4	0.6	0.4	2.3	0.2
Mean	79.4	75.8	19.9	1.2	0.4	2.5	0.3	60.1	15.8	0.9	0.3	1.9	0.2
S.D.	10.6	3.9	3.9	0.2	0.1	0.6	0.1	8.2	4.1	0.3	0.1	0.4	0.1

LUC: Large unstained cells

Appendix 6-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 200

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
3001	907	15.7	45.8	50.4	17.3	34.4	2.8	97.5	16.0	18.2	261
3002	836	14.9	43.2	51.7	17.9	34.5	2.0	111.1	15.1	17.8	253
3003	919	15.8	45.4	49.4	17.2	34.8	2.4	120.1	15.1	19.1	254
3004	921	16.0	46.2	50.2	17.4	34.7	2.1	113.7	15.2	17.8	285
3005	920	15.5	43.6	47.4	16.8	35.5	2.3	121.2	13.9	16.9	270
Mean	901	15.6	44.8	49.8	17.3	34.8	2.3	112.7	15.1	18.0	265
S.D.	37	0.4	1.4	1.6	0.4	0.4	0.3	9.5	0.8	0.8	13

Appendix 6-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 200

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3001	66.4	76.6	19.4	1.1	0.5	2.0	0.4	50.9	12.9	0.7	0.3	1.3	0.3
3002	92.6	79.9	14.5	1.2	0.8	3.2	0.4	74.0	13.4	1.1	0.7	3.0	0.4
3003	78.5	74.9	19.6	1.6	0.4	3.2	0.3	58.8	15.4	1.3	0.3	2.5	0.2
3004	79.0	71.7	23.6	1.4	0.3	2.5	0.5	56.7	18.6	1.1	0.2	2.0	0.4
3005	60.7	74.2	22.3	1.0	0.6	1.6	0.2	45.1	13.6	0.6	0.4	1.0	0.1
Mean	75.4	75.5	19.9	1.3	0.5	2.5	0.4	57.1	14.8	1.0	0.4	2.0	0.3
S.D.	12.4	3.0	3.5	0.2	0.2	0.7	0.1	10.9	2.3	0.3	0.2	0.8	0.1

LUC: Large unstained cells

Appendix 6-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 1000

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4001	884	15.8	44.2	50.0	17.8	35.6	1.8	100.4	18.6	19.1	248
4002	924	14.4	42.1	45.6	15.6	34.2	3.1	130.6	14.9	18.6	275
4003	878	15.8	44.9	51.1	18.0	35.2	2.7	97.5	19.6	18.6	241
4004	878	15.9	45.0	51.2	18.1	35.3	2.4	112.5	20.6	19.7	225
4005	927	16.3	47.0	50.7	17.6	34.7	2.1	101.8	19.2	21.3	263
Mean	898	15.6	44.6	49.7	17.4	35.0	2.4	108.6	18.6	19.5	250
S.D.	25	0.7	1.8	2.4	1.0	0.6	0.5	13.6	2.2	1.1	19

Appendix 6-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of administration)
Dose (mg/kg): 1000

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4001	103.2	75.4	20.2	1.6	0.4	2.2	0.2	77.8	20.9	1.6	0.4	2.3	0.2
4002	125.9	68.3	26.6	1.1	0.4	3.3	0.3	86.1	33.5	1.4	0.5	4.1	0.4
4003	113.2	62.4	32.7	1.0	0.3	3.2	0.3	70.7	37.0	1.1	0.4	3.7	0.3
4004	83.2	72.5	22.8	1.3	0.3	2.8	0.3	60.3	19.0	1.1	0.2	2.3	0.3
4005	49.9	81.9	14.4	0.7	0.8	1.9	0.3	40.9	7.2	0.4	0.4	0.9	0.1
Mean	95.1	72.1	23.3	1.1	0.4	2.7	0.3	67.2	23.5	1.1	0.4	2.7	0.3
S.D.	29.7	7.3	6.9	0.3	0.2	0.6	0.0	17.5	12.0	0.5	0.1	1.3	0.1

LUC: Large unstained cells

Appendix 6-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1102	695	13.1	38.1	54.8	18.9	34.5	7.6	127.2	10.9	12.4	210
1104	804	14.9	43.5	54.1	18.5	34.3	4.6	120.6	12.4	20.2	298
1105	723	13.4	38.7	53.5	18.6	34.7	6.9	143.9	11.8	13.7	254
1107a)	431Z	8.0Z	22.2Z	51.5Z	18.5Z	35.9Z	9.4Z	117.4Z	10.6Z	11.9Z	438Z
1111	617	12.3	36.8	59.7	19.9	33.4	8.8	117.5	12.0	14.7	281
1112	729	13.8	39.5	54.2	19.0	35.1	5.8	145.7	11.2	16.2	272
Mean	714	13.5	39.3	55.3	19.0	34.4	6.7	131.0	11.7	15.4	263
S.D.	67	1.0	2.5	2.5	0.6	0.6	1.6	13.1	0.6	3.0	34

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 6-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1102	119.2	63.7	32.1	0.9	0.2	2.6	0.5	76.0	38.2	1.0	0.2	3.1	0.6
1104	100.9	66.6	28.9	1.3	0.3	2.4	0.7	67.2	29.1	1.3	0.3	2.4	0.7
1105	110.0	66.8	29.7	0.5	0.1	2.5	0.3	73.4	32.7	0.6	0.1	2.8	0.3
1107a)	66.4Z	42.4Z	49.2Z	1.2Z	0.2Z	6.1Z	0.9Z	28.2Z	32.7Z	0.8Z	0.1Z	4.1Z	0.6Z
1111	111.2	62.7	32.7	0.3	0.1	3.5	0.6	69.7	36.3	0.4	0.2	3.9	0.7
1112	137.9	49.0	45.8	1.3	0.3	3.4	0.3	67.6	63.1	1.7	0.4	4.7	0.4
Mean	115.8	61.8	33.8	0.9	0.2	2.9	0.5	70.8	39.9	1.0	0.2	3.4	0.5
S.D.	13.9	7.4	6.9	0.5	0.1	0.5	0.2	3.8	13.4	0.5	0.1	0.9	0.2

LUC: Large unstained cells
a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 6-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 40

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
2101	655	12.9	37.0	56.4	19.6	34.8	7.6	121.9	11.1	11.9	239
2102	728	13.1	38.5	52.9	18.0	34.0	5.1	110.0	11.1	13.1	274
2104	773	14.6	42.9	55.5	18.9	34.0	3.7	146.2	12.7	13.6	225
2105	708	13.2	38.0	53.6	18.6	34.8	8.2	148.2	11.3	13.5	291
2108	713	14.0	40.4	56.7	19.6	34.6	8.8	177.5	11.3	12.8	262
2109a)	770Z	14.4Z	40.3Z	52.3Z	18.7Z	35.8Z	3.1Z	104.6Z	11.7Z	14.5Z	154Z
2110a)	814Z	14.9Z	42.0Z	51.6Z	18.3Z	35.4Z	1.6Z	115.4Z	12.7Z	12.6Z	210Z
2112b)	777Z	15.1Z	42.3Z	54.5Z	19.4Z	35.7Z	3.1Z	119.7Z	12.9Z	17.6Z	230Z
Mean	715	13.6	39.4	55.0	18.9	34.4	6.7	140.8	11.5	13.0	258
S.D.	42	0.7	2.3	1.7	0.7	0.4	2.2	26.2	0.7	0.7	27

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 6-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 40

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
2101	92.4	57.9	38.0	0.5	0.2	3.1	0.4	53.5	35.2	0.4	0.2	2.8	0.4
2102	132.4	45.3	49.6	0.7	0.3	4.0	0.2	59.9	65.6	0.9	0.4	5.3	0.3
2104	111.6	74.5	17.7	2.6	0.3	4.2	0.6	83.2	19.8	2.9	0.4	4.7	0.7
2105	118.6	58.9	37.0	0.8	0.2	2.9	0.3	69.8	43.8	0.9	0.2	3.4	0.3
2108	112.5	56.8	37.1	0.6	0.4	4.7	0.3	63.9	41.8	0.6	0.5	5.3	0.4
2109a)	52.3Z	85.1Z	10.2Z	1.3Z	0.3Z	2.8Z	0.2Z	44.5Z	5.3Z	0.7Z	0.2Z	1.4Z	0.1Z
2110a)	59.2Z	86.5Z	8.5Z	2.2Z	0.4Z	1.9Z	0.5Z	51.3Z	5.0Z	1.3Z	0.2Z	1.1Z	0.3Z
2112b)	93.6Z	73.3Z	20.4Z	1.4Z	0.3Z	3.3Z	1.4Z	68.6Z	19.1Z	1.3Z	0.2Z	3.1Z	1.3Z
Mean	113.5	58.7	35.9	1.0	0.3	3.8	0.4	66.1	41.2	1.1	0.3	4.3	0.4
S.D.	14.4	10.4	11.5	0.9	0.1	0.8	0.2	11.3	16.6	1.0	0.1	1.1	0.2

LUC: Large unstained cells
a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 6-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 200

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
3102	644	12.8	37.2	57.7	19.9	34.6	8.2	131.7	11.8	14.4	250
3104	667	12.9	37.5	56.2	19.4	34.4	8.7	159.9	11.4	13.9	309
3105	723	14.2	40.0	55.3	19.7	35.5	8.0	124.7	12.4	14.1	253
3106	730	14.1	40.7	55.8	19.3	34.6	6.7	140.4	13.5	14.3	198
3109	704	13.0	38.1	54.1	18.5	34.2	7.6	132.6	11.6	15.0	382
3110a)	822Z	14.6Z	41.5Z	50.5Z	17.8Z	35.2Z	2.6Z	108.3Z	12.2Z	12.0Z	176Z
Mean	694	13.4	38.7	55.8	19.4	34.7	7.8	137.9	12.1	14.3	278
S.D.	37	0.7	1.6	1.3	0.5	0.5	0.8	13.5	0.8	0.4	70

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 6-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 200

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
3102	110.0	51.6	44.4	0.7	0.1	2.6	0.4	56.7	48.9	0.8	0.2	2.9	0.5
3104	97.2	47.9	47.3	1.2	0.2	3.2	0.2	46.5	45.9	1.2	0.2	3.1	0.2
3105	96.7	63.7	29.4	2.0	0.3	4.2	0.4	61.6	28.4	1.9	0.3	4.1	0.3
3106	99.5	64.7	31.2	1.2	0.3	2.4	0.3	64.3	31.0	1.2	0.3	2.4	0.3
3109	135.6	56.2	40.4	0.7	0.2	1.9	0.6	76.1	54.8	1.0	0.3	2.6	0.8
3110a)	66.0Z	88.7Z	7.7Z	1.1Z	0.3Z	1.6Z	0.6Z	58.6Z	5.1Z	0.7Z	0.2Z	1.0Z	0.4Z
Mean	107.8	56.8	38.5	1.2	0.2	2.9	0.4	61.0	41.8	1.2	0.3	3.0	0.4
S.D.	16.4	7.4	7.9	0.5	0.1	0.9	0.1	10.8	11.5	0.4	0.1	0.7	0.2

LUC: Large unstained cells
a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 6-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 1000

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4101	697	14.0	40.3	57.8	20.2	34.9	8.9	134.3	11.2	14.5	333
4104	677	13.8	39.4	58.2	20.3	34.9	6.6	119.8	13.0	14.4	234
4105	693	13.7	39.3	56.7	19.8	34.8	8.7	143.8	11.1	13.0	227
4107	755	14.0	40.2	53.3	18.6	34.9	7.1	122.9	13.0	15.6	254
4108	699	13.9	39.2	56.1	19.9	35.4	6.9	144.1	10.7	15.8	252
Mean	704	13.9	39.7	56.4	19.8	35.0	7.6	133.0	11.8	14.7	260
S.D.	30	0.1	0.5	1.9	0.7	0.2	1.1	11.4	1.1	1.1	42

Appendix 6-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Lactation day 5)
Dose (mg/kg): 1000

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4101	102.5	53.5	44.0	0.9	0.2	1.0	0.4	54.8	45.0	1.0	0.2	1.0	0.4
4104	137.3	57.5	37.7	1.1	0.4	3.0	0.4	78.9	51.8	1.5	0.5	4.1	0.5
4105	88.7	52.8	40.8	1.2	0.3	4.5	0.3	46.9	36.2	1.1	0.3	4.0	0.3
4107	151.4	59.9	35.3	0.6	0.4	3.5	0.3	90.7	53.4	1.0	0.6	5.3	0.5
4108	166.0	54.3	40.3	1.2	0.4	3.5	0.3	90.1	66.9	1.9	0.6	5.8	0.6
Mean	129.2	55.6	39.6	1.0	0.3	3.1	0.3	72.3	50.7	1.3	0.4	4.0	0.5
S.D.	32.7	3.0	3.3	0.3	0.1	1.3	0.1	20.3	11.3	0.4	0.2	1.9	0.1

LUC: Large unstained cells

Appendix 6-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1113	792	15.4	43.9	55.4	19.4	35.0	3.0	106.9	11.2	14.7	185
1114	805	15.3	42.8	53.2	19.0	35.7	2.3	105.4	12.1	18.7	207
1115	812	14.9	41.9	51.7	18.4	35.5	2.5	105.4	11.8	14.5	176
1116	806	15.0	41.7	51.7	18.6	36.0	1.8	128.3	11.6	12.5	194
1117	818	15.3	43.5	53.2	18.7	35.0	2.2	105.1	11.7	16.1	184
Mean	807	15.2	42.8	53.0	18.8	35.4	2.4	110.2	11.7	15.3	189
S.D.	10	0.2	1.0	1.5	0.4	0.4	0.4	10.1	0.3	2.3	12

Appendix 6-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1113	72.8	82.7	11.5	0.7	0.4	3.7	1.0	60.3	8.4	0.5	0.3	2.7	0.7
1114	59.1	86.0	10.1	1.4	0.5	1.6	0.4	50.8	6.0	0.8	0.3	1.0	0.2
1115	35.5	78.3	16.2	2.2	0.3	2.4	0.5	27.8	5.7	0.8	0.1	0.8	0.2
1116	52.4	76.9	16.9	2.7	0.4	2.7	0.4	40.3	8.9	1.4	0.2	1.4	0.2
1117	47.2	73.7	20.0	2.1	0.4	3.5	0.3	34.8	9.5	1.0	0.2	1.7	0.1
Mean	53.4	79.5	14.9	1.8	0.4	2.8	0.5	42.8	7.7	0.9	0.2	1.5	0.3
S.D.	13.9	4.9	4.1	0.8	0.1	0.9	0.3	12.9	1.7	0.3	0.1	0.7	0.2

LUC: Large unstained cells

Appendix 6-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4113	763	14.6	40.3	52.8	19.1	36.1	2.4	124.2	10.8	13.8	185
4114	807	15.3	42.3	52.3	19.0	36.2	2.2	119.2	11.9	19.1	163
4115	773	14.8	41.2	53.3	19.1	35.9	2.7	109.8	10.9	14.9	164
4116	785	14.6	41.7	53.1	18.6	35.0	2.3	101.9	12.1	15.3	139
4117	809	15.3	42.3	52.3	19.0	36.2	2.5	106.0	12.5	16.4	141
Mean	787	14.9	41.6	52.8	19.0	35.9	2.4	112.2	11.6	15.9	158
S.D.	20	0.4	0.8	0.5	0.2	0.5	0.2	9.3	0.8	2.0	19

Appendix 6-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4113	97.1	85.7	10.8	1.2	0.3	1.3	0.8	83.2	10.5	1.1	0.3	1.2	0.8
4114	54.6	76.1	19.8	1.5	0.5	1.9	0.3	41.6	10.8	0.8	0.3	1.0	0.1
4115	54.8	83.6	12.7	1.0	0.3	1.5	1.0	45.8	7.0	0.5	0.2	0.8	0.5
4116	79.8	79.4	16.1	1.3	0.2	2.5	0.5	63.4	12.8	1.1	0.2	2.0	0.4
4117	101.5	75.1	20.2	1.4	0.5	2.3	0.6	76.2	20.4	1.4	0.5	2.4	0.6
Mean	77.6	80.0	15.9	1.3	0.4	1.9	0.6	62.0	12.3	1.0	0.3	1.5	0.5
S.D.	22.4	4.6	4.2	0.2	0.1	0.5	0.3	18.2	5.0	0.3	0.1	0.7	0.3

LUC: Large unstained cells

Appendix 6-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1008	913	16.6	46.9	51.4	18.2	35.4	2.3	89.4	17.5	19.3	254
1009	899	17.3	48.0	53.4	19.2	36.1	1.5	97.9	16.4	20.4	273
1010	935	17.2	47.4	50.7	18.4	36.3	1.6	93.8	15.7	23.2	246
1011	941	16.3	45.6	48.5	17.3	35.8	1.2	97.0	15.9	17.2	300
1012	940	17.0	48.1	51.2	18.1	35.4	1.8	96.3	12.7	18.8	234
Mean	926	16.9	47.2	51.0	18.2	35.8	1.7	94.9	15.6	19.8	261
S.D.	19	0.4	1.0	1.8	0.7	0.4	0.4	3.4	1.8	2.2	26

Appendix 6-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1008	88.1	80.2	15.4	1.8	0.5	1.6	0.4	70.7	13.6	1.6	0.4	1.4	0.3
1009	71.9	81.8	13.1	1.9	0.4	2.5	0.3	58.8	9.4	1.4	0.3	1.8	0.2
1010	93.3	79.3	16.5	1.1	0.4	2.2	0.4	74.0	15.4	1.0	0.4	2.1	0.4
1011	81.0	78.8	13.3	1.7	0.3	4.5	1.4	63.8	10.8	1.4	0.2	3.7	1.1
1012	59.4	82.1	12.6	2.6	0.5	1.9	0.4	48.7	7.5	1.5	0.3	1.1	0.2
Mean	78.7	80.4	14.2	1.8	0.4	2.5	0.6	63.2	11.3	1.4	0.3	2.0	0.4
S.D.	13.5	1.5	1.7	0.5	0.1	1.1	0.5	10.0	3.2	0.2	0.1	1.0	0.4

LUC: Large unstained cells

Appendix 6-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 1000

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4008	940	17.0	47.4	50.4	18.1	35.9	2.1	90.5	17.1	20.0	335
4009	903	16.3	44.8	49.6	18.0	36.3	2.1	106.6	18.5	20.2	229
4010	864	15.7	44.9	52.0	18.2	35.0	2.2	108.9	13.6	18.8	253
4011	952	16.6	45.9	48.3	17.4	36.1	1.7	105.9	14.4	17.7	234
4012	941	16.9	48.6	51.7	18.0	34.8	1.6	86.4	15.3	19.4	243
Mean	920	16.5	46.3	50.4	17.9	35.6	1.9	99.7	15.8	19.2	259
S.D.	36	0.5	1.6	1.5	0.3	0.7	0.3	10.4	2.0	1.0	44

Appendix 6-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of male rats (End of recovery)
Dose (mg/kg): 1000

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4008	107.9	81.1	15.1	0.9	0.5	1.9	0.4	87.5	16.2	1.0	0.6	2.1	0.4
4009	75.3	77.6	17.2	1.7	0.5	2.7	0.3	58.4	12.9	1.3	0.4	2.0	0.2
4010	125.7	81.0	13.1	1.9	0.6	2.3	1.1	101.8	16.5	2.4	0.7	2.8	1.4
4011	68.0	79.1	15.7	1.0	0.2	2.8	1.2	53.8	10.7	0.7	0.2	1.9	0.8
4012	58.7	73.7	20.1	1.8	0.4	3.1	0.9	43.3	11.8	1.1	0.2	1.8	0.5
Mean	87.1	78.5	16.2	1.5	0.4	2.6	0.8	69.0	13.6	1.3	0.4	2.1	0.7
S.D.	28.4	3.1	2.6	0.5	0.2	0.5	0.4	24.6	2.6	0.7	0.2	0.4	0.5

LUC: Large unstained cells

Appendix 6-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
1118	842	15.9	43.8	52.0	18.9	36.3	1.7	102.8	11.7	14.8	195
1119	789	15.1	43.0	54.5	19.2	35.2	2.1	116.0	11.5	13.7	181
1120	827	15.3	42.3	51.1	18.5	36.1	2.0	130.1	12.4	13.8	223
1121	796	15.0	41.4	52.0	18.8	36.2	1.8	122.9	12.7	16.5	170
1122	820	15.4	42.8	52.1	18.8	36.1	1.9	109.1	11.7	13.1	167
Mean	815	15.3	42.7	52.3	18.8	36.0	1.9	116.2	12.0	14.4	187
S.D.	22	0.4	0.9	1.3	0.3	0.4	0.2	10.8	0.5	1.3	23

Appendix 6-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
1118	81.0	87.1	9.4	1.0	0.3	1.6	0.6	70.5	7.6	0.8	0.3	1.3	0.5
1119	81.7	86.3	9.2	1.3	0.2	2.2	0.8	70.5	7.5	1.0	0.2	1.8	0.7
1120	48.8	66.4	29.4	1.2	0.2	2.5	0.3	32.4	14.3	0.6	0.1	1.2	0.1
1121	52.0	76.3	18.3	1.7	0.2	2.8	0.7	39.7	9.5	0.9	0.1	1.4	0.4
1122	42.1	82.5	13.1	1.1	0.5	2.4	0.3	34.8	5.5	0.5	0.2	1.0	0.1
Mean	61.1	79.7	15.9	1.3	0.3	2.3	0.5	49.6	8.9	0.8	0.2	1.3	0.4
S.D.	18.8	8.6	8.4	0.3	0.1	0.4	0.2	19.3	3.3	0.2	0.1	0.3	0.3

LUC: Large unstained cells

Appendix 6-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 1000

Animal number	RBC 10E4/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	Retic %	PLT 10E4/μL	PT s	APTT s	FIB mg/dL
4118	812	15.3	42.6	52.4	18.8	36.0	2.3	103.1	11.5	13.5	152
4119	810	15.0	42.1	52.0	18.5	35.5	2.6	110.6	11.8	15.9	184
4120	857	15.6	43.7	51.0	18.2	35.6	1.8	127.7	12.5	16.6	184
4121	810	15.2	42.2	52.1	18.8	36.1	1.8	96.0	12.5	14.5	189
4122	763	14.8	40.8	53.4	19.4	36.3	2.7	110.5	12.7	18.8	212
Mean	810	15.2	42.3	52.2	18.7	35.9	2.2	109.6	12.2	15.9	184
S.D.	33	0.3	1.0	0.9	0.4	0.3	0.4	11.8	0.5	2.0	21

Appendix 6-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual hematology of female rats (End of recovery)
Dose (mg/kg): 1000

Animal number	WBC	Differential leukocyte ratio (%)						Differential leukocyte counts (10E2/μL)					
	10E2/μL	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
4118	43.5	86.5	9.6	1.3	0.3	1.6	0.7	37.7	4.2	0.6	0.1	0.7	0.3
4119	51.4	83.5	11.6	1.1	0.2	3.2	0.4	42.9	6.0	0.6	0.1	1.7	0.2
4120	57.4	74.8	19.1	1.9	0.4	3.2	0.5	43.0	11.0	1.1	0.3	1.8	0.3
4121	70.2	61.6	33.1	1.4	0.4	3.1	0.3	43.3	23.3	1.0	0.3	2.2	0.2
4122	104.5	81.7	13.4	1.3	0.4	2.6	0.6	85.4	14.0	1.3	0.4	2.7	0.6
Mean	65.4	77.6	17.4	1.4	0.3	2.7	0.5	50.5	11.7	0.9	0.2	1.8	0.3
S.D.	23.9	9.9	9.5	0.3	0.1	0.7	0.2	19.7	7.6	0.3	0.1	0.7	0.2

LUC: Large unstained cells

Appendix 7-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1001	60	30	47	1	514	6.4	42	17	68	0.0	119
1002	69	32	40	0	331	18.5	56	52	91	0.1	123
1003	58	27	38	0	427	10.4	44	18	67	0.1	162
1004	73	33	34	0	374	4.9	46	17	70	0.0	106
1005	73	36	52	1	428	9.9	48	17	73	0.1	126
Mean	67	32	42	0	415	10.0	47	24	74	0.1	127
S.D.	7	3	7	1	69	5.3	5	16	10	0.1	21

Appendix 7-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1001	15	0.32	142	4.7	107	9.4	5.8	5.6	3.1	1.24
1002	14	0.27	143	4.7	106	9.6	5.5	5.9	3.4	1.36
1003	20	0.28	142	4.5	107	9.4	5.7	5.6	3.2	1.33
1004	15	0.27	144	4.5	110	9.7	5.6	5.7	3.1	1.19
1005	13	0.24	142	4.6	107	9.9	6.2	6.0	3.6	1.50
Mean	15	0.28	143	4.6	107	9.6	5.8	5.8	3.3	1.32
S.D.	3	0.03	1	0.1	2	0.2	0.3	0.2	0.2	0.12

Appendix 7-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 40

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2001	68	32	48	0	338	8.2	54	61	92	0.0	134
2002	79	29	36	1	358	5.2	39	20	63	0.1	111
2003	87	52	41	0	342	5.7	36	17	64	0.1	115
2004	74	37	35	1	399	12.9	52	18	77	0.1	106
2005	60	26	63	0	284	12.0	39	48	67	0.0	126
Mean	74	35	45	0	344	8.8	44	33	73	0.1	118
S.D.	10	10	12	1	41	3.5	8	20	12	0.1	11

Appendix 7-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 40

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
2001	14	0.29	142	4.9	105	9.3	5.3	5.4	2.9	1.16
2002	15	0.28	144	4.8	108	9.4	5.3	5.7	3.2	1.28
2003	14	0.23	145	4.6	109	9.6	5.6	5.5	3.2	1.39
2004	16	0.28	143	4.4	107	9.5	5.3	5.8	3.3	1.32
2005	13	0.21	144	4.6	105	9.9	6.0	5.9	3.2	1.19
Mean	14	0.26	144	4.7	107	9.5	5.5	5.7	3.2	1.27
S.D.	1	0.04	1	0.2	2	0.2	0.3	0.2	0.2	0.09

Appendix 7-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 200

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3001	68	26	38	0	321	4.2	41	32	74	0.1	143
3002	75	33	47	0	463	15.8	56	30	87	0.1	128
3003	56	25	36	0	420	16.8	53	32	79	0.1	109
3004	71	28	38	0	367	7.0	36	16	62	0.0	116
3005	70	29	35	1	408	7.7	50	19	73	0.0	112
Mean	68	28	39	0	396	10.3	47	26	75	0.1	122
S.D.	7	3	5	0	54	5.6	8	8	9	0.1	14

Appendix 7-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 200

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
3001	15	0.27	140	4.7	106	9.0	5.3	5.4	3.2	1.45
3002	17	0.28	142	4.5	106	9.4	6.9	5.6	3.0	1.15
3003	13	0.22	141	4.6	103	9.9	5.8	6.1	3.5	1.35
3004	16	0.28	143	4.6	107	9.5	6.4	5.6	3.2	1.33
3005	16	0.27	144	4.6	107	9.6	6.2	6.0	3.2	1.14
Mean	15	0.26	142	4.6	106	9.5	6.1	5.7	3.2	1.28
S.D.	2	0.03	2	0.1	2	0.3	0.6	0.3	0.2	0.13

Appendix 7-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 1000

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4001	70	31	40	0	296	21.0	43	44	82	0.0	113
4002	79	49	62	1	390	34.4	60	30	94	0.0	126
4003	64	26	31	0	374	8.5	47	60	86	0.0	105
4004	72	32	39	0	340	38.6	40	27	75	0.0	116
4005	59	26	34	0	263	20.6	52	39	77	0.0	128
Mean	69	33	41	0	333	24.6	48	40	83	0.0	118
S.D.	8	9	12	0	53	12.0	8	13	8	0.0	10

Appendix 7-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of administration)
Dose (mg/kg): 1000

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4001	15	0.26	139	3.8	100	9.3	5.2	5.5	3.2	1.39
4002	17	0.26	140	3.8	99	9.6	5.4	5.9	3.2	1.19
4003	14	0.22	144	4.0	104	9.8	5.8	5.5	3.4	1.62
4004	13	0.23	143	4.6	107	9.7	5.6	5.4	3.3	1.57
4005	16	0.25	143	4.5	102	9.2	6.1	5.4	3.1	1.35
Mean	15	0.24	142	4.1	102	9.5	5.6	5.5	3.2	1.42
S.D.	2	0.02	2	0.4	3	0.3	0.3	0.2	0.1	0.17

Appendix 7-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1102	71	47	52	0	147	11.3	71	94	142	0.1	112
1104	81	46	47	1	304	61.1	56	37	113	0.1	102
1105	141	51	64	1	293	8.4	46	57	95	0.0	128
1107a)	41Z	17Z	57Z	1Z	172Z	11.4Z	65Z	35Z	123Z	0.0Z	172Z
1111	93	74	44	1	407	11.7	61	82	123	0.1	132
1112	82	50	44	1	175	11.8	51	45	99	0.1	120
Mean	94	54	50	1	265	20.9	57	63	114	0.1	119
S.D.	28	12	8	0	105	22.5	10	24	19	0.0	12

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 7-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1102	14	0.26	139	3.8	107	10.3	5.2	6.1	3.8	1.65
1104	17	0.29	140	4.1	106	10.2	6.2	6.2	3.5	1.30
1105	14	0.30	140	3.7	108	9.8	6.0	5.6	3.5	1.67
1107a)	26Z	0.33Z	137Z	4.7Z	103Z	9.7Z	4.5Z	5.3Z	3.2Z	1.52Z
1111	14	0.26	141	4.3	107	9.9	5.3	5.9	3.3	1.27
1112	13	0.25	140	4.3	103	10.2	7.7	5.8	3.5	1.52
Mean	14	0.27	140	4.0	106	10.1	6.1	5.9	3.5	1.48
S.D.	2	0.02	1	0.3	2	0.2	1.0	0.2	0.2	0.19

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 7-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 40

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
2101	67	45	36	0	332	16.0	61	46	127	0.1	129
2102	98	72	37	1	175	6.8	72	32	130	0.1	127
2104	111	46	45	0	210	15.3	40	25	78	0.0	113
2105	86	57	46	0	202	12.4	64	59	129	0.1	132
2108	84	44	47	0	365	13.5	35	35	70	0.1	119
2109a)	46Z	34Z	55Z	0Z	447Z	7.9Z	76Z	141Z	170Z	0.0Z	162Z
2110a)	45Z	30Z	43Z	1Z	529Z	40.7Z	66Z	108Z	137Z	0.1Z	167Z
2112b)	71Z	48Z	52Z	1Z	313Z	17.0Z	89Z	66Z	160Z	0.1Z	157Z
Mean	89	53	42	0	257	12.8	54	39	107	0.1	124
S.D.	16	12	5	0	86	3.6	16	13	30	0.0	8

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 7-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 40

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
2101	15	0.31	140	4.0	105	10.1	6.4	6.1	3.7	1.54
2102	17	0.38	138	3.9	103	10.3	6.6	6.4	3.6	1.29
2104	18	0.32	142	4.3	109	10.0	6.1	5.8	3.3	1.32
2105	18	0.22	140	4.5	108	10.1	6.4	6.5	3.9	1.50
2108	15	0.26	140	4.2	106	9.7	6.3	5.4	3.2	1.45
2109a)	23Z	0.22Z	139Z	4.7Z	104Z	10.4Z	5.2Z	6.5Z	3.9Z	1.50Z
2110a)	22Z	0.25Z	143Z	3.9Z	109Z	10.7Z	4.6Z	6.3Z	3.9Z	1.63Z
2112b)	19Z	0.28Z	142Z	4.1Z	105Z	10.6Z	4.0Z	6.2Z	3.5Z	1.30Z
Mean	17	0.30	140	4.2	106	10.0	6.4	6.0	3.5	1.42
S.D.	2	0.06	1	0.2	2	0.2	0.2	0.5	0.3	0.11

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 7-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 200

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
3102	104	62	42	0	248	14.4	70	55	144	0.0	130
3104	98	59	47	1	177	14.8	70	55	138	0.1	118
3105	73	43	39	1	175	28.6	72	61	133	0.1	123
3106	70	39	70	1	171	11.2	33	22	78	0.1	136
3109	88	55	47	0	307	20.7	45	53	97	0.1	132
3110a)	51Z	40Z	53Z	1Z	354Z	58.0Z	57Z	101Z	134Z	0.1Z	158Z
Mean	87	52	49	1	216	17.9	58	49	118	0.1	128
S.D.	15	10	12	1	60	6.9	18	15	29	0.0	7

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 7-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 200

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
3102	17	0.28	140	4.0	104	10.0	6.6	6.5	3.8	1.41
3104	14	0.24	141	4.6	106	10.7	8.1	6.4	3.8	1.46
3105	15	0.25	139	4.1	104	10.1	6.5	6.0	3.7	1.61
3106	15	0.29	140	4.6	108	9.8	6.3	6.2	3.7	1.48
3109	15	0.24	140	4.5	107	9.9	7.1	5.9	3.6	1.57
3110a)	21Z	0.26Z	142Z	4.0Z	104Z	10.3Z	4.5Z	6.6Z	4.0Z	1.54Z
Mean	15	0.26	140	4.4	106	10.1	6.9	6.2	3.7	1.51
S.D.	1	0.02	1	0.3	2	0.4	0.7	0.3	0.1	0.08

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 7-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 1000

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4101	121	69	39	1	371	17.3	58	68	123	0.1	102
4104	91	48	35	0	325	26.6	37	41	84	0.1	135
4105	99	56	60	1	403	21.2	63	74	129	0.0	123
4107	90	40	43	1	188	34.0	59	59	117	0.1	117
4108	105	62	51	1	356	14.0	56	43	121	0.0	104
Mean	101	55	46	1	329	22.6	55	57	115	0.1	116
S.D.	13	11	10	0	83	7.9	10	15	18	0.1	14

Appendix 7-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Lactation day 5)
Dose (mg/kg): 1000

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4101	16	0.23	139	3.9	104	10.1	6.7	6.0	3.6	1.50
4104	15	0.27	139	4.2	106	9.9	5.7	5.9	3.5	1.46
4105	17	0.23	141	4.3	105	10.5	8.5	6.3	3.7	1.42
4107	22	0.29	137	4.2	102	9.9	7.5	5.9	3.5	1.46
4108	17	0.25	137	4.4	101	10.6	8.8	6.2	3.7	1.48
Mean	17	0.25	139	4.2	104	10.2	7.4	6.1	3.6	1.46
S.D.	3	0.03	2	0.2	2	0.3	1.3	0.2	0.1	0.03

Appendix 7-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1113	57	28	41	1	161	23.0	74	15	136	0.1	130
1114	65	23	63	1	169	9.9	46	15	91	0.1	135
1115	70	34	33	1	177	9.2	82	17	133	0.1	110
1116	364	232	178	1	140	35.5	61	17	116	0.1	125
1117	70	30	34	0	229	21.2	73	28	142	0.1	129
Mean	125	69	70	1	175	19.8	67	18	124	0.1	126
S.D.	134	91	62	0	33	10.8	14	5	21	0.0	10

Appendix 7-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1113	16	0.31	142	4.4	108	9.9	3.7	6.6	4.1	1.64
1114	16	0.33	141	4.6	109	9.4	3.4	5.7	3.5	1.59
1115	17	0.32	142	4.1	108	9.6	4.2	6.3	3.6	1.33
1116	19	0.35	143	4.4	108	10.1	4.4	6.4	3.9	1.56
1117	16	0.34	142	4.8	109	9.9	3.9	6.1	3.9	1.77
Mean	17	0.33	142	4.5	108	9.8	3.9	6.2	3.8	1.58
S.D.	1	0.02	1	0.3	1	0.3	0.4	0.3	0.2	0.16

Appendix 7-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4113	46	18	40	1	127	8.9	61	26	115	0.0	144
4114	51	17	36	1	190	15.1	64	23	127	0.0	125
4115	66	25	39	1	316	31.3	59	21	122	0.0	132
4116	63	17	39	0	168	19.2	67	34	133	0.0	148
4117	56	22	41	0	131	10.5	59	18	116	0.0	125
Mean	56	20	39	1	186	17.0	62	24	123	0.0	135
S.D.	8	4	2	1	77	9.0	3	6	8	0.0	11

Appendix 7-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4113	19	0.36	138	4.7	106	9.4	4.0	5.7	3.4	1.48
4114	17	0.30	140	4.1	103	9.4	4.0	5.7	3.5	1.59
4115	19	0.38	140	4.2	107	9.9	4.4	6.2	4.0	1.82
4116	17	0.34	143	3.4	104	9.6	3.8	5.9	3.7	1.68
4117	18	0.28	140	3.8	105	9.7	4.2	6.2	3.8	1.58
Mean	18	0.33	140	4.0	105	9.6	4.1	5.9	3.7	1.63
S.D.	1	0.04	2	0.5	2	0.2	0.2	0.3	0.2	0.13

Appendix 7-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1008	65	29	43	0	317	8.5	39	51	69	0.1	107
1009	58	28	43	0	386	5.6	53	34	81	0.1	110
1010	59	33	41	0	322	8.1	37	77	78	0.1	112
1011	71	33	58	1	342	7.2	39	30	68	0.1	112
1012	61	28	38	0	272	8.2	40	26	70	0.1	123
Mean	63	30	45	0	328	7.5	42	44	73	0.1	113
S.D.	5	3	8	0	41	1.2	6	21	6	0.0	6

Appendix 7-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1008	14	0.31	142	4.6	104	9.6	6.1	5.6	3.2	1.33
1009	13	0.28	141	4.7	106	9.5	5.7	5.7	3.2	1.28
1010	15	0.25	142	4.4	105	9.7	6.0	6.0	3.4	1.31
1011	16	0.26	143	4.5	107	9.7	5.8	6.2	3.3	1.14
1012	18	0.28	142	4.3	105	9.5	5.7	5.8	3.2	1.23
Mean	15	0.28	142	4.5	105	9.6	5.9	5.9	3.3	1.26
S.D.	2	0.02	1	0.2	1	0.1	0.2	0.2	0.1	0.08

Appendix 7-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 1000

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4008	64	31	39	0	322	17.0	50	27	79	0.1	109
4009	61	32	38	1	265	7.1	47	44	76	0.0	126
4010	74	29	48	0	263	19.5	65	40	96	0.1	134
4011	58	22	41	1	255	12.2	44	40	74	0.1	114
4012	55	25	43	1	304	12.3	38	18	62	0.1	116
Mean	62	28	42	1	282	13.6	49	34	77	0.1	120
S.D.	7	4	4	1	29	4.8	10	11	12	0.0	10

Appendix 7-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of male rats (End of recovery)
Dose (mg/kg): 1000

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4008	16	0.23	142	4.6	105	9.5	6.5	6.1	3.1	1.03
4009	16	0.25	142	4.8	108	9.0	5.5	5.3	3.1	1.41
4010	16	0.26	142	4.4	104	9.9	5.8	6.1	3.4	1.26
4011	16	0.27	142	4.7	107	9.6	6.2	5.7	3.2	1.28
4012	18	0.25	143	4.7	108	9.5	5.4	5.6	3.2	1.33
Mean	16	0.25	142	4.6	106	9.5	5.9	5.8	3.2	1.26
S.D.	1	0.01	0	0.2	2	0.3	0.5	0.3	0.1	0.14

Appendix 7-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
1118	62	29	39	1	290	6.6	82	21	135	0.1	114
1119	55	35	38	0	132	9.9	77	20	137	0.1	104
1120	63	29	31	2	263	11.3	72	18	126	0.1	134
1121	73	41	38	1	142	19.4	44	13	88	0.1	122
1122	70	37	43	1	128	19.8	66	24	122	0.1	160
Mean	65	34	38	1	191	13.4	68	19	122	0.1	127
S.D.	7	5	4	1	79	5.9	15	4	20	0.0	22

Appendix 7-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 0

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
1118	16	0.36	141	4.5	108	10.2	4.4	6.3	3.7	1.42
1119	16	0.32	142	4.5	109	10.0	4.1	6.1	3.8	1.65
1120	23	0.34	140	4.3	108	9.5	3.4	6.2	3.5	1.30
1121	19	0.30	140	4.6	107	9.8	4.8	6.0	3.7	1.61
1122	18	0.29	141	4.3	108	10.3	3.9	6.6	4.0	1.54
Mean	18	0.32	141	4.4	108	10.0	4.1	6.2	3.7	1.50
S.D.	3	0.03	1	0.1	1	0.3	0.5	0.2	0.2	0.14

Appendix 7-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 1000

Animal number	AST IU/L	ALT IU/L	LDH IU/L	r-GTP IU/L	ALP IU/L	TBA µmol/L	T-CHO mg/dL	TG mg/dL	PL mg/dL	T-BIL mg/dL	GLU mg/dL
4118	52	23	41	1	136	9.6	56	15	104	0.1	126
4119	55	23	42	0	118	8.4	80	40	143	0.1	128
4120	58	37	35	2	111	8.3	58	21	107	0.1	118
4121	58	27	35	1	135	12.6	81	25	145	0.1	132
4122	65	29	33	1	124	12.9	65	54	134	0.1	152
Mean	58	28	37	1	125	10.4	68	31	127	0.1	131
S.D.	5	6	4	1	11	2.2	12	16	20	0.0	13

Appendix 7-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual blood chemistry of female rats (End of recovery)
Dose (mg/kg): 1000

Animal number	BUN mg/dL	CRNN mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	ALB g/dL	A/G
4118	17	0.33	140	4.7	107	9.7	2.8	6.0	3.6	1.50
4119	17	0.32	140	4.4	106	10.0	3.1	6.4	3.9	1.56
4120	18	0.29	140	4.4	107	10.0	3.4	6.3	3.7	1.42
4121	24	0.33	139	4.1	106	9.3	4.0	6.3	3.5	1.25
4122	17	0.34	139	4.2	105	9.8	4.1	6.0	3.7	1.61
Mean	19	0.32	140	4.4	106	9.8	3.5	6.2	3.7	1.47
S.D.	3	0.02	1	0.2	1	0.3	0.6	0.2	0.1	0.14

Appendix 8-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1001	483	2.22	12.4	10.4	11.7	22.1	350
	1002	528	2.07	13.6	14.4	14.2	28.6	299
	1003	496	2.17	12.9	12.0	11.1	23.1	460
	1004	494	2.05	12.4	11.6	12.5	24.1	278
	1005	508	2.19	15.1	13.0	11.1	24.1	327
	1006	511	2.21	15.3	6.3	12.4	18.7	275
	1007	489	2.03	13.5	15.2	13.0	28.2	177
	Mean	501	2.13	13.6	11.8	12.3	24.1	309
	S.D.	15	0.08	1.2	2.9	1.1	3.4	86
Relative	1001		0.46	2.6	2.2	2.4	4.6	72
	1002		0.39	2.6	2.7	2.7	5.4	57
	1003		0.44	2.6	2.4	2.2	4.7	93
	1004		0.41	2.5	2.3	2.5	4.9	56
	1005		0.43	3.0	2.6	2.2	4.7	64
	1006		0.43	3.0	1.2	2.4	3.7	54
	1007		0.42	2.8	3.1	2.7	5.8	36
	Mean		0.43	2.7	2.4	2.4	4.8	62
	S.D.		0.02	0.2	0.6	0.2	0.7	18

Appendix 8-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1001	1.33	11.82	0.65	1.56	1.60	3.16
	1002	1.37	12.42	0.68	1.65	1.67	3.32
	1003	1.41	12.33	0.88	1.64	1.77	3.41
	1004	1.43	12.90	0.71	1.64	1.85	3.49
	1005	1.61	12.41	0.85	1.71	1.71	3.42
	1006	1.39	13.00	0.66	1.71	1.73	3.44
	1007	1.53	11.68	0.62	1.67	1.64	3.31
	Mean	1.44	12.37	0.72	1.65	1.71	3.36
	S.D.	0.10	0.49	0.10	0.05	0.08	0.11
Relative	1001	0.28	2.45	0.13	0.32	0.33	0.65
	1002	0.26	2.35	0.13	0.31	0.32	0.63
	1003	0.28	2.49	0.18	0.33	0.36	0.69
	1004	0.29	2.61	0.14	0.33	0.37	0.71
	1005	0.32	2.44	0.17	0.34	0.34	0.67
	1006	0.27	2.54	0.13	0.33	0.34	0.67
	1007	0.31	2.39	0.13	0.34	0.34	0.68
	Mean	0.29	2.47	0.14	0.33	0.34	0.67
	S.D.	0.02	0.09	0.02	0.01	0.02	0.03

Appendix 8-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	1001	37	33	70	1.64	1.61	3.25
	1002	28	28	56	1.76	1.65	3.41
	1003	27	30	57	1.80	1.81	3.61
	1004	30	29	59	1.61	1.63	3.24
	1005	28	33	61	1.83	1.86	3.69
	1006	34	33	67	1.77	1.71	3.48
	1007	38	36	74	1.51	1.54	3.05
	Mean	32	32	63	1.70	1.69	3.39
	S.D.	5	3	7	0.12	0.11	0.23
Relative	1001	8	7	14	0.34	0.33	0.67
	1002	5	5	11	0.33	0.31	0.65
	1003	5	6	11	0.36	0.36	0.73
	1004	6	6	12	0.33	0.33	0.66
	1005	6	6	12	0.36	0.37	0.73
	1006	7	6	13	0.35	0.33	0.68
	1007	8	7	15	0.31	0.31	0.62
	Mean	6	6	13	0.34	0.33	0.68
	S.D.	1	1	2	0.02	0.02	0.04

Appendix 8-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 0

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	1001	633	607	1240	1.47	1.21
	1002	681	635	1316	1.69	1.56
	1003	697	700	1397	1.34	1.10
	1004	661	630	1291	2.20	1.41
	1005	691	728	1419	1.89	1.35
	1006	699	697	1396	1.65	1.18
	1007	637	612	1249	1.77	1.19
	Mean	671	658	1330	1.72	1.29
	S.D.	28	49	74	0.28	0.16
Relative	1001	131	126	257	0.30	0.25
	1002	129	120	249	0.32	0.30
	1003	141	141	282	0.27	0.22
	1004	134	128	261	0.45	0.29
	1005	136	143	279	0.37	0.27
	1006	137	136	273	0.32	0.23
	1007	130	125	255	0.36	0.24
	Mean	134	131	265	0.34	0.26
	S.D.	4	9	13	0.06	0.03

Appendix 8-5 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 40

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	2001	519	2.06	13.5	9.5	7.4	16.9	225
	2002	459	2.17	12.5	14.3	12.0	26.3	312
	2003	448	2.22	14.1	11.6	10.3	21.9	201
	2004	435	2.09	11.6	13.0	12.0	25.0	365
	2005	532	2.23	13.8	10.6	10.5	21.1	346
	2006	476	2.03	12.2	14.3	11.3	25.6	312
	2007	473	2.07	13.1	17.4	14.8	32.2	327
	2008	448	2.09	11.9	11.4	9.6	21.0	159
	2009	580	2.17	15.1	9.6	9.5	19.1	187
	2010	484	2.09	15.0	12.7	13.4	26.1	259
	2011	468	2.04	13.7	18.3	13.2	31.5	273
	2012	507	2.13	15.3	15.8	17.7	33.5	325
	Mean	486	2.12	13.5	13.2	11.8	25.0	274
	S.D.	42	0.07	1.3	2.9	2.7	5.3	68
Relative	2001		0.40	2.6	1.8	1.4	3.3	43
	2002		0.47	2.7	3.1	2.6	5.7	68
	2003		0.50	3.1	2.6	2.3	4.9	45
	2004		0.48	2.7	3.0	2.8	5.7	84
	2005		0.42	2.6	2.0	2.0	4.0	65
	2006		0.43	2.6	3.0	2.4	5.4	66
	2007		0.44	2.8	3.7	3.1	6.8	69
	2008		0.47	2.7	2.5	2.1	4.7	35
	2009		0.37	2.6	1.7	1.6	3.3	32
	2010		0.43	3.1	2.6	2.8	5.4	54
	2011		0.44	2.9	3.9	2.8	6.7	58
	2012		0.42	3.0	3.1	3.5	6.6	64
	Mean		0.44	2.8	2.8	2.5	5.2	57
	S.D.		0.04	0.2	0.7	0.6	1.2	16

Appendix 8-6 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 40

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	2001	1.61	12.38	0.78	1.55	1.81	3.36
	2002	1.42	10.16	0.71	1.58	1.66	3.24
	2003	1.46	10.68	0.85	1.86	1.87	3.73
	2004	1.23	9.64	0.61	1.43	1.58	3.01
	2005	1.38	13.71	0.91	1.99	2.16	4.15
	2006	1.46	11.80	0.62	1.62	1.68	3.30
	2007	1.41	11.23	0.71	1.69	1.75	3.44
	2008	1.39	11.06	0.67	1.62	1.64	3.26
	2009	1.81	16.08	0.78	1.90	2.07	3.97
	2010	1.56	11.46	0.70	1.74	1.67	3.41
	2011	1.49	11.31	0.79	1.87	2.00	3.87
	2012	1.46	14.08	1.02	1.81	1.80	3.61
	Mean	1.47	11.97	0.76	1.72	1.81	3.53
	S.D.	0.14	1.83	0.12	0.17	0.18	0.34
Relative	2001	0.31	2.39	0.15	0.30	0.35	0.65
	2002	0.31	2.21	0.15	0.34	0.36	0.71
	2003	0.33	2.38	0.19	0.42	0.42	0.83
	2004	0.28	2.22	0.14	0.33	0.36	0.69
	2005	0.26	2.58	0.17	0.37	0.41	0.78
	2006	0.31	2.48	0.13	0.34	0.35	0.69
	2007	0.30	2.37	0.15	0.36	0.37	0.73
	2008	0.31	2.47	0.15	0.36	0.37	0.73
	2009	0.31	2.77	0.13	0.33	0.36	0.68
	2010	0.32	2.37	0.14	0.36	0.35	0.70
	2011	0.32	2.42	0.17	0.40	0.43	0.83
	2012	0.29	2.78	0.20	0.36	0.36	0.71
	Mean	0.30	2.45	0.16	0.36	0.37	0.73
	S.D.	0.02	0.18	0.02	0.03	0.03	0.06

Appendix 8-7 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 40

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	2001	34	33	67	1.69	1.65	3.34
	2002	30	30	60	1.49	1.45	2.94
	2003	25	26	51	1.57	1.59	3.16
	2004	26	24	50	1.68	1.60	3.28
	2005	34	36	70	1.73	1.68	3.41
	2006	28	35	63	1.42	1.53	2.95
	2007	26	27	53	1.62	1.69	3.31
	2008	24	28	52	1.66	1.66	3.32
	2009	40	41	81	1.89	1.81	3.70
	2010	32	34	66	1.79	1.79	3.58
	2011	30	38	68	1.80	1.84	3.64
	2012	35	35	70	1.78	1.74	3.52
	Mean	30	32	63	1.68	1.67	3.35
	S.D.	5	5	10	0.14	0.12	0.25
Relative	2001	7	6	13	0.33	0.32	0.64
	2002	7	7	13	0.32	0.32	0.64
	2003	6	6	11	0.35	0.35	0.71
	2004	6	6	11	0.39	0.37	0.75
	2005	6	7	13	0.33	0.32	0.64
	2006	6	7	13	0.30	0.32	0.62
	2007	5	6	11	0.34	0.36	0.70
	2008	5	6	12	0.37	0.37	0.74
	2009	7	7	14	0.33	0.31	0.64
	2010	7	7	14	0.37	0.37	0.74
	2011	6	8	15	0.38	0.39	0.78
	2012	7	7	14	0.35	0.34	0.69
	Mean	6	7	13	0.35	0.35	0.69
	S.D.	1	1	1	0.03	0.03	0.05

Appendix 8-8 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 40

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	2001	662	678	1340	1.60	1.30
	2002	600	599	1199	1.62	1.25
	2003	651	636	1287	1.88	1.41
	2004	593	587	1180	1.49	1.03
	2005	648	640	1288	1.44	1.10
	2006	524	600	1124	1.32	1.36
	2007	651	663	1314	1.46	0.97
	2008	633	632	1265	1.69	1.28
	2009	656	604	1260	1.38	1.33
	2010	762	790	1552	2.15	1.52
	2011	673	664	1337	2.59	1.61
	2012	672	683	1355	1.83	1.22
	Mean	644	648	1292	1.70	1.28
	S.D.	57	55	108	0.37	0.19
Relative	2001	128	131	258	0.31	0.25
	2002	131	131	261	0.35	0.27
	2003	145	142	287	0.42	0.31
	2004	136	135	271	0.34	0.24
	2005	122	120	242	0.27	0.21
	2006	110	126	236	0.28	0.29
	2007	138	140	278	0.31	0.21
	2008	141	141	282	0.38	0.29
	2009	113	104	217	0.24	0.23
	2010	157	163	321	0.44	0.31
	2011	144	142	286	0.55	0.34
	2012	133	135	267	0.36	0.24
	Mean	133	134	267	0.35	0.27
	S.D.	14	14	27	0.09	0.04

Appendix 8-9 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 200

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	3001	469	2.04	13.3	7.2	8.0	15.2	151
	3002	488	2.12	13.0	11.3	10.0	21.3	262
	3003	528	2.14	17.5	9.0	10.6	19.6	465
	3004	443	2.08	13.8	11.0	7.2	18.2	309
	3005	472	2.06	11.8	12.6	13.1	25.7	229
	3006	516	2.21	14.9	12.6	11.5	24.1	243
	3007	471	2.25	14.3	14.7	9.6	24.3	228
	3008	460	2.20	12.6	10.8	13.0	23.8	305
	3009	495	2.05	16.1	12.2	11.1	23.3	256
	3010	482	2.10	13.1	16.1	12.7	28.8	276
	3011	450	1.96	16.3	12.9	12.5	25.4	314
	3012	407	2.14	11.7	13.0	6.9	19.9	282
	Mean	473	2.11	14.0	12.0	10.5	22.5	277
	S.D.	33	0.08	1.8	2.4	2.2	3.8	74
Relative	3001		0.43	2.8	1.5	1.7	3.2	32
	3002		0.43	2.7	2.3	2.0	4.4	54
	3003		0.41	3.3	1.7	2.0	3.7	88
	3004		0.47	3.1	2.5	1.6	4.1	70
	3005		0.44	2.5	2.7	2.8	5.4	49
	3006		0.43	2.9	2.4	2.2	4.7	47
	3007		0.48	3.0	3.1	2.0	5.2	48
	3008		0.48	2.7	2.3	2.8	5.2	66
	3009		0.41	3.3	2.5	2.2	4.7	52
	3010		0.44	2.7	3.3	2.6	6.0	57
	3011		0.44	3.6	2.9	2.8	5.6	70
	3012		0.53	2.9	3.2	1.7	4.9	69
	Mean		0.45	3.0	2.5	2.2	4.8	59
	S.D.		0.03	0.3	0.6	0.4	0.8	15

Appendix 8-10 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 200

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	3001	1.43	11.17	0.61	1.59	1.69	3.28
	3002	1.46	12.64	0.72	1.61	1.70	3.31
	3003	1.87	14.84	0.92	1.88	2.04	3.92
	3004	1.26	10.92	0.72	1.55	1.63	3.18
	3005	1.37	12.23	0.72	1.82	1.72	3.54
	3006	1.50	12.54	0.88	2.00	2.02	4.02
	3007	1.30	11.59	0.81	1.68	1.49	3.17
	3008	1.39	10.98	0.66	1.56	1.63	3.19
	3009	1.45	11.11	0.76	1.87	1.86	3.73
	3010	1.37	11.02	0.87	1.70	1.72	3.42
	3011	1.20	10.19	0.68	1.73	1.77	3.50
	3012	1.33	9.92	0.70	1.68	1.74	3.42
	Mean	1.41	11.60	0.75	1.72	1.75	3.47
	S.D.	0.17	1.32	0.10	0.14	0.16	0.29
Relative	3001	0.30	2.38	0.13	0.34	0.36	0.70
	3002	0.30	2.59	0.15	0.33	0.35	0.68
	3003	0.35	2.81	0.17	0.36	0.39	0.74
	3004	0.28	2.47	0.16	0.35	0.37	0.72
	3005	0.29	2.59	0.15	0.39	0.36	0.75
	3006	0.29	2.43	0.17	0.39	0.39	0.78
	3007	0.28	2.46	0.17	0.36	0.32	0.67
	3008	0.30	2.39	0.14	0.34	0.35	0.69
	3009	0.29	2.24	0.15	0.38	0.38	0.75
	3010	0.28	2.29	0.18	0.35	0.36	0.71
	3011	0.27	2.26	0.15	0.38	0.39	0.78
	3012	0.33	2.44	0.17	0.41	0.43	0.84
	Mean	0.30	2.45	0.16	0.37	0.37	0.73
	S.D.	0.02	0.16	0.01	0.02	0.03	0.05

Appendix 8-11 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 200

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	3001	25	25	50	1.64	1.68	3.32
	3002	29	30	59	1.75	1.74	3.49
	3003	32	34	66	1.76	1.69	3.45
	3004	35	37	72	1.68	1.70	3.38
	3005	24	25	49	1.60	1.64	3.24
	3006	32	36	68	1.64	1.64	3.28
	3007	35	37	72	1.57	1.63	3.20
	3008	33	35	68	1.85	1.71	3.56
	3009	32	32	64	1.78	1.79	3.57
	3010	30	34	64	1.57	1.57	3.14
	3011	29	32	61	1.62	1.62	3.24
	3012	24	25	49	1.44	1.47	2.91
	Mean	30	32	62	1.66	1.66	3.32
	S.D.	4	5	8	0.11	0.08	0.19
Relative	3001	5	5	11	0.35	0.36	0.71
	3002	6	6	12	0.36	0.36	0.72
	3003	6	6	13	0.33	0.32	0.65
	3004	8	8	16	0.38	0.38	0.76
	3005	5	5	10	0.34	0.35	0.69
	3006	6	7	13	0.32	0.32	0.64
	3007	7	8	15	0.33	0.35	0.68
	3008	7	8	15	0.40	0.37	0.77
	3009	6	6	13	0.36	0.36	0.72
	3010	6	7	13	0.33	0.33	0.65
	3011	6	7	14	0.36	0.36	0.72
	3012	6	6	12	0.35	0.36	0.71
	Mean	6	7	13	0.35	0.35	0.70
	S.D.	1	1	2	0.02	0.02	0.04

Appendix 8-12 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 200

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	3001	615	644	1259	1.84	1.21
	3002	682	696	1378	2.12	1.20
	3003	711	683	1394	1.67	1.27
	3004	691	669	1360	2.04	1.81
	3005	627	626	1253	1.43	1.11
	3006	712	697	1409	2.37	2.17
	3007	594	606	1200	1.79	1.74
	3008	750	639	1389	2.03	1.29
	3009	672	679	1351	1.87	1.27
	3010	594	606	1200	1.58	1.18
	3011	629	675	1304	1.78	0.98
	3012	671	665	1336	1.76	1.38
	Mean	662	657	1319	1.86	1.38
	S.D.	50	32	75	0.25	0.34
Relative	3001	131	137	268	0.39	0.26
	3002	140	143	282	0.43	0.25
	3003	135	129	264	0.32	0.24
	3004	156	151	307	0.46	0.41
	3005	133	133	265	0.30	0.24
	3006	138	135	273	0.46	0.42
	3007	126	129	255	0.38	0.37
	3008	163	139	302	0.44	0.28
	3009	136	137	273	0.38	0.26
	3010	123	126	249	0.33	0.24
	3011	140	150	290	0.40	0.22
	3012	165	163	328	0.43	0.34
	Mean	141	139	280	0.39	0.29
	S.D.	14	11	23	0.05	0.07

Appendix 8-13 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4001	445	2.07	12.4	13.2	11.1	24.3	262
	4002	494	2.03	11.9	11.0	11.5	22.5	153
	4003	506	2.17	12.6	11.3	10.7	22.0	485
	4004	467	2.19	12.8	14.3	11.5	25.8	347
	4005	457	2.25	13.7	10.3	10.6	20.9	234
	4006	485	2.19	16.5	11.6	11.6	23.2	389
	4007	485	2.15	13.9	15.4	13.3	28.7	317
	Mean	477	2.15	13.4	12.4	11.5	23.9	312
	S.D.	22	0.08	1.5	1.9	0.9	2.6	109
Relative	4001		0.47	2.8	3.0	2.5	5.5	59
	4002		0.41	2.4	2.2	2.3	4.6	31
	4003		0.43	2.5	2.2	2.1	4.3	96
	4004		0.47	2.7	3.1	2.5	5.5	74
	4005		0.49	3.0	2.3	2.3	4.6	51
	4006		0.45	3.4	2.4	2.4	4.8	80
	4007		0.44	2.9	3.2	2.7	5.9	65
	Mean		0.45	2.8	2.6	2.4	5.0	65
	S.D.		0.03	0.3	0.4	0.2	0.6	21

Appendix 8-14 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 1000

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4001	1.45	12.35	0.82	1.62	1.71	3.33
	4002	1.47	13.66	0.85	1.60	1.82	3.42
	4003	1.68	13.32	0.82	1.89	2.12	4.01
	4004	1.34	11.26	0.66	1.78	1.79	3.57
	4005	1.29	11.07	0.62	2.02	1.97	3.99
	4006	1.35	14.48	0.84	1.90	2.03	3.93
	4007	1.51	13.38	0.78	1.88	1.93	3.81
	Mean	1.44	12.79	0.77	1.81	1.91	3.72
	S.D.	0.13	1.27	0.09	0.16	0.14	0.28
Relative	4001	0.33	2.78	0.18	0.36	0.38	0.75
	4002	0.30	2.77	0.17	0.32	0.37	0.69
	4003	0.33	2.63	0.16	0.37	0.42	0.79
	4004	0.29	2.41	0.14	0.38	0.38	0.76
	4005	0.28	2.42	0.14	0.44	0.43	0.87
	4006	0.28	2.99	0.17	0.39	0.42	0.81
	4007	0.31	2.76	0.16	0.39	0.40	0.79
	Mean	0.30	2.68	0.16	0.38	0.40	0.78
	S.D.	0.02	0.21	0.02	0.04	0.02	0.06

Appendix 8-15 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 1000

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	4001	32	35	67	1.52	1.56	3.08
	4002	34	34	68	1.69	1.67	3.36
	4003	23	23	46	1.35	1.34	2.69
	4004	25	26	51	1.67	1.68	3.35
	4005	30	34	64	1.69	1.74	3.43
	4006	28	32	60	1.74	1.71	3.45
	4007	27	32	59	1.82	1.76	3.58
	Mean	28	31	59	1.64	1.64	3.28
	S.D.	4	5	8	0.16	0.15	0.30
Relative	4001	7	8	15	0.34	0.35	0.69
	4002	7	7	14	0.34	0.34	0.68
	4003	5	5	9	0.27	0.26	0.53
	4004	5	6	11	0.36	0.36	0.72
	4005	7	7	14	0.37	0.38	0.75
	4006	6	7	12	0.36	0.35	0.71
	4007	6	7	12	0.38	0.36	0.74
	Mean	6	7	12	0.35	0.34	0.69
	S.D.	1	1	2	0.04	0.04	0.07

Appendix 8-16 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of administration)
Dose (mg/kg): 1000

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	4001	609	648	1257	1.59	1.23
	4002	689	668	1357	1.84	1.04
	4003	603	580	1183	2.06	1.30
	4004	679	660	1339	1.90	1.28
	4005	685	665	1350	1.66	1.39
	4006	614	651	1265	1.81	1.38
	4007	726	692	1418	1.85	1.59
	Mean	658	652	1310	1.82	1.32
	S.D.	49	35	79	0.15	0.17
Relative	4001	137	146	282	0.36	0.28
	4002	139	135	275	0.37	0.21
	4003	119	115	234	0.41	0.26
	4004	145	141	287	0.41	0.27
	4005	150	146	295	0.36	0.30
	4006	127	134	261	0.37	0.28
	4007	150	143	292	0.38	0.33
	Mean	138	137	275	0.38	0.28
	S.D.	12	11	21	0.02	0.04

Appendix 8-17 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1101	344	2.02	18.5	11.0	8.8	19.8	179
	1102	330	1.86	21.2	10.8	10.0	20.8	248
	1103	300	2.01	18.5	9.7	9.5	19.2	292
	1104	311	2.05	15.8	13.4	11.7	25.1	268
	1105	308	1.94	16.3	7.7	9.3	17.0	330
	1106	347	2.19	20.6	6.9	8.1	15.0	241
	1107a)	303Z	1.93Z	16.5Z	5.7Z	5.3Z	11.0Z	143Z
	1108	333	1.95	19.8	9.3	6.5	15.8	200
	1109	310	2.02	20.8	11.0	7.6	18.6	197
	1110	300	1.95	17.7	9.9	9.7	19.6	168
	1111	298	2.02	25.4	8.0	10.7	18.7	138
	1112	312	1.97	15.2	9.5	8.8	18.3	231
	Mean	318	2.00	19.1	9.7	9.2	18.9	227
	S.D.	18	0.08	2.9	1.8	1.4	2.7	57
Relative	1101		0.59	5.4	3.2	2.6	5.8	52
	1102		0.56	6.4	3.3	3.0	6.3	75
	1103		0.67	6.2	3.2	3.2	6.4	97
	1104		0.66	5.1	4.3	3.8	8.1	86
	1105		0.63	5.3	2.5	3.0	5.5	107
	1106		0.63	5.9	2.0	2.3	4.3	69
	1107a)		0.64Z	5.4Z	1.9Z	1.7Z	3.6Z	47Z
	1108		0.59	5.9	2.8	2.0	4.7	60
	1109		0.65	6.7	3.5	2.5	6.0	64
	1110		0.65	5.9	3.3	3.2	6.5	56
	1111		0.68	8.5	2.7	3.6	6.3	46
	1112		0.63	4.9	3.0	2.8	5.9	74
	Mean		0.63	6.0	3.1	2.9	6.0	71
	S.D.		0.04	1.0	0.6	0.5	1.0	19

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 8-18 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1101	0.92	10.98	0.59	1.13	1.15	2.28
	1102	1.04	10.78	0.73	1.03	1.07	2.10
	1103	1.04	10.75	0.60	1.00	1.04	2.04
	1104	1.11	10.37	0.61	1.18	1.15	2.33
	1105	1.05	9.71	0.66	0.98	1.03	2.01
	1106	1.34	11.93	0.80	1.23	1.21	2.44
	1107a)	0.98Z	10.57Z	0.55Z	1.02Z	1.05Z	2.07Z
	1108	1.02	10.87	0.70	1.29	1.26	2.55
	1109	1.13	10.68	0.75	1.17	1.08	2.25
	1110	1.00	9.71	0.60	1.21	1.18	2.39
	1111	1.12	10.60	0.73	1.08	0.97	2.05
	1112	0.95	10.78	0.66	1.13	1.15	2.28
	Mean	1.07	10.65	0.68	1.13	1.12	2.25
	S.D.	0.11	0.61	0.07	0.10	0.09	0.18
Relative	1101	0.27	3.19	0.17	0.33	0.33	0.66
	1102	0.32	3.27	0.22	0.31	0.32	0.64
	1103	0.35	3.58	0.20	0.33	0.35	0.68
	1104	0.36	3.33	0.20	0.38	0.37	0.75
	1105	0.34	3.15	0.21	0.32	0.33	0.65
	1106	0.39	3.44	0.23	0.35	0.35	0.70
	1107a)	0.32Z	3.49Z	0.18Z	0.34Z	0.35Z	0.68Z
	1108	0.31	3.26	0.21	0.39	0.38	0.77
	1109	0.36	3.45	0.24	0.38	0.35	0.73
	1110	0.33	3.24	0.20	0.40	0.39	0.80
	1111	0.38	3.56	0.24	0.36	0.33	0.69
	1112	0.30	3.46	0.21	0.36	0.37	0.73
	Mean	0.34	3.36	0.21	0.36	0.35	0.71
	S.D.	0.04	0.15	0.02	0.03	0.02	0.05

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 8-19 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1101	46	44	90	39.7	41.7	81.4	605
	1102	45	44	89	52.7	46.3	99.0	712
	1103	34	38	72	57.8	63.3	121.1	572
	1104	33	40	73	61.6	52.6	114.2	572
	1105	36	38	74	53.6	56.7	110.3	645
	1106	42	46	88	75.1	88.0	163.1	971
	1107a)	48Z	48Z	96Z	50.3Z	69.3Z	119.6Z	1971Z
	1108	40	45	85	51.5	51.5	103.0	517
	1109	49	51	100	51.0	54.9	105.9	615
	1110	36	39	75	47.7	60.1	107.8	673
	1111	39	43	82	50.5	48.5	99.0	742
	1112	42	50	92	40.6	57.6	98.2	685
	Mean	40	43	84	52.9	56.5	109.4	664
	S.D.	5	4	9	9.8	12.2	20.6	122
Relative	1101	13	13	26	11.5	12.1	23.7	176
	1102	14	13	27	16.0	14.0	30.0	216
	1103	11	13	24	19.3	21.1	40.4	191
	1104	11	13	23	19.8	16.9	36.7	184
	1105	12	12	24	17.4	18.4	35.8	209
	1106	12	13	25	21.6	25.4	47.0	280
	1107a)	16Z	16Z	32Z	16.6Z	22.9Z	39.5Z	650Z
	1108	12	14	26	15.5	15.5	30.9	155
	1109	16	16	32	16.5	17.7	34.2	198
	1110	12	13	25	15.9	20.0	35.9	224
	1111	13	14	28	16.9	16.3	33.2	249
	1112	13	16	29	13.0	18.5	31.5	220
	Mean	13	14	26	16.7	17.8	34.5	209
	S.D.	1	1	3	2.9	3.6	6.0	35

a): Necropsied on lactation day 0 because all pups were stillborn
Z: Data was excluded from statistical analysis.

Appendix 8-20 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 40

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	2101	354	2.07	23.2	7.7	8.8	16.5	161
	2102	325	2.05	22.5	9.1	6.3	15.4	166
	2103	307	2.06	24.0	9.0	9.5	18.5	147
	2104	311	2.01	17.1	10.4	9.8	20.2	292
	2105	298	1.90	16.7	6.5	8.9	15.4	179
	2106	306	1.88	16.0	6.2	6.5	12.7	116
	2107	336	2.01	17.9	10.3	9.3	19.6	183
	2108	336	2.03	19.2	11.7	8.0	19.7	243
	2109a)	289Z	1.99Z	17.4Z	9.5Z	7.9Z	17.4Z	299Z
	2110a)	319Z	2.02Z	14.9Z	6.3Z	8.0Z	14.3Z	396Z
	2111	304	2.02	19.4	11.8	9.3	21.1	158
	2112b)	294Z	1.96Z	16.8Z	8.3Z	6.5Z	14.8Z	273Z
	Mean	320	2.00	19.6	9.2	8.5	17.7	183
	S.D.	19	0.07	3.0	2.1	1.3	2.8	53
Relative	2101		0.58	6.6	2.2	2.5	4.7	45
	2102		0.63	6.9	2.8	1.9	4.7	51
	2103		0.67	7.8	2.9	3.1	6.0	48
	2104		0.65	5.5	3.3	3.2	6.5	94
	2105		0.64	5.6	2.2	3.0	5.2	60
	2106		0.61	5.2	2.0	2.1	4.2	38
	2107		0.60	5.3	3.1	2.8	5.8	54
	2108		0.60	5.7	3.5	2.4	5.9	72
	2109a)		0.69Z	6.0Z	3.3Z	2.7Z	6.0Z	103Z
	2110a)		0.63Z	4.7Z	2.0Z	2.5Z	4.5Z	124Z
	2111		0.66	6.4	3.9	3.1	6.9	52
	2112b)		0.67Z	5.7Z	2.8Z	2.2Z	5.0Z	93Z
	Mean		0.63	6.1	2.9	2.7	5.5	57
	S.D.		0.03	0.9	0.6	0.5	0.9	17

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 8-21 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 40

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	2101	1.11	13.06	0.82	1.17	1.31	2.48
	2102	1.02	10.43	0.59	1.04	0.98	2.02
	2103	1.17	10.55	0.69	1.07	0.98	2.05
	2104	1.03	9.05	0.66	1.24	1.18	2.42
	2105	0.98	10.97	0.57	1.05	1.02	2.07
	2106	1.08	10.20	0.54	0.88	0.85	1.73
	2107	1.18	10.92	0.79	1.36	1.30	2.66
	2108	1.10	10.80	0.76	1.08	1.07	2.15
	2109a)	0.93Z	10.31Z	0.50Z	1.14Z	1.12Z	2.26Z
	2110a)	1.04Z	10.75Z	0.48Z	1.07Z	1.06Z	2.13Z
	2111	1.01	10.79	0.63	0.99	0.96	1.95
	2112b)	1.05Z	9.75Z	0.47Z	0.98Z	0.95Z	1.93Z
	Mean	1.08	10.75	0.67	1.10	1.07	2.17
	S.D.	0.07	1.05	0.10	0.14	0.16	0.29
Relative	2101	0.31	3.69	0.23	0.33	0.37	0.70
	2102	0.31	3.21	0.18	0.32	0.30	0.62
	2103	0.38	3.44	0.22	0.35	0.32	0.67
	2104	0.33	2.91	0.21	0.40	0.38	0.78
	2105	0.33	3.68	0.19	0.35	0.34	0.69
	2106	0.35	3.33	0.18	0.29	0.28	0.57
	2107	0.35	3.25	0.24	0.40	0.39	0.79
	2108	0.33	3.21	0.23	0.32	0.32	0.64
	2109a)	0.32Z	3.57Z	0.17Z	0.39Z	0.39Z	0.78Z
	2110a)	0.33Z	3.37Z	0.15Z	0.34Z	0.33Z	0.67Z
	2111	0.33	3.55	0.21	0.33	0.32	0.64
	2112b)	0.36Z	3.32Z	0.16Z	0.33Z	0.32Z	0.66Z
	Mean	0.34	3.36	0.21	0.34	0.34	0.68
	S.D.	0.02	0.25	0.02	0.04	0.04	0.07

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 8-22 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 40

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	2101	43	45	88	68.5	55.1	123.6	936
	2102	41	45	86	60.3	55.9	116.2	563
	2103	40	42	82	45.9	52.4	98.3	674
	2104	38	40	78	54.3	47.1	101.4	634
	2105	31	36	67	39.4	48.7	88.1	636
	2106	31	35	66	55.8	56.8	112.6	683
	2107	47	56	103	60.9	66.3	127.2	655
	2108	44	48	92	60.8	44.8	105.6	670
	2109a)	28Z	30Z	58Z	55.5Z	49.2Z	104.7Z	818Z
	2110a)	30Z	30Z	60Z	64.3Z	64.6Z	128.9Z	926Z
	2111	41	44	85	49.8	56.8	106.6	590
	2112b)	26Z	29Z	55Z	56.6Z	44.8Z	101.4Z	811Z
	Mean	40	43	83	55.1	53.8	108.8	671
	S.D.	5	6	12	8.9	6.5	12.4	107
Relative	2101	12	13	25	19.4	15.6	34.9	264
	2102	13	14	26	18.6	17.2	35.8	173
	2103	13	14	27	15.0	17.1	32.0	220
	2104	12	13	25	17.5	15.1	32.6	204
	2105	10	12	22	13.2	16.3	29.6	213
	2106	10	11	22	18.2	18.6	36.8	223
	2107	14	17	31	18.1	19.7	37.9	195
	2108	13	14	27	18.1	13.3	31.4	199
	2109a)	10Z	10Z	20Z	19.2Z	17.0Z	36.2Z	283Z
	2110a)	9Z	9Z	19Z	20.2Z	20.3Z	40.4Z	290Z
	2111	13	14	28	16.4	18.7	35.1	194
	2112b)	9Z	10Z	19Z	19.3Z	15.2Z	34.5Z	276Z
	Mean	12	14	26	17.2	16.8	34.0	209
	S.D.	1	2	3	2.0	2.0	2.7	25

a): Non-pregnant
b): Not copulated
Z: Data was excluded from statistical analysis.

Appendix 8-23 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 200

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	3101	351	2.04	21.3	8.4	6.8	15.2	283
	3102	315	2.05	24.9	10.7	9.2	19.9	239
	3103	325	2.07	20.8	12.3	10.0	22.3	284
	3104	326	1.98	18.1	11.4	7.7	19.1	158
	3105	335	1.98	19.6	8.4	9.1	17.5	227
	3106	297	2.04	15.4	8.0	5.4	13.4	243
	3107	343	2.07	24.2	13.6	12.6	26.2	344
	3108	299	2.01	18.5	8.6	9.7	18.3	131
	3109	306	1.94	19.2	10.4	12.0	22.4	143
	3110a)	305Z	1.92Z	16.4Z	7.1Z	8.9Z	16.0Z	253Z
	3111	306	2.08	19.2	10.7	9.6	20.3	222
	3112	320	2.07	19.0	12.0	9.5	21.5	196
	Mean	320	2.03	20.0	10.4	9.2	19.6	225
	S.D.	18	0.05	2.7	1.9	2.1	3.6	65
Relative	3101		0.58	6.1	2.4	1.9	4.3	81
	3102		0.65	7.9	3.4	2.9	6.3	76
	3103		0.64	6.4	3.8	3.1	6.9	87
	3104		0.61	5.6	3.5	2.4	5.9	48
	3105		0.59	5.9	2.5	2.7	5.2	68
	3106		0.69	5.2	2.7	1.8	4.5	82
	3107		0.60	7.1	4.0	3.7	7.6	100
	3108		0.67	6.2	2.9	3.2	6.1	44
	3109		0.63	6.3	3.4	3.9	7.3	47
	3110a)		0.63Z	5.4Z	2.3Z	2.9Z	5.2Z	83Z
	3111		0.68	6.3	3.5	3.1	6.6	73
	3112		0.65	5.9	3.8	3.0	6.7	61
	Mean		0.64	6.3	3.3	2.9	6.1	70
	S.D.		0.04	0.7	0.6	0.7	1.1	18

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 8-24 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 200

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	3101	1.11	12.14	0.82	1.38	1.43	2.81
	3102	1.17	10.88	0.55	1.15	1.11	2.26
	3103	0.97	10.86	0.71	1.09	1.01	2.10
	3104	1.01	11.18	0.62	1.26	1.21	2.47
	3105	1.11	10.71	0.75	1.13	1.19	2.32
	3106	0.88	9.41	0.59	1.02	0.89	1.91
	3107	1.17	10.72	0.58	1.23	1.23	2.46
	3108	0.97	10.43	0.61	1.07	1.02	2.09
	3109	1.01	10.34	0.96	1.10	1.14	2.24
	3110a)	0.98Z	10.82Z	0.48Z	1.03Z	1.04Z	2.07Z
	3111	1.15	10.40	0.64	1.05	1.00	2.05
	3112	1.08	13.02	0.89	1.29	1.29	2.58
	Mean	1.06	10.92	0.70	1.16	1.14	2.30
	S.D.	0.10	0.96	0.14	0.11	0.15	0.26
Relative	3101	0.32	3.46	0.23	0.39	0.41	0.80
	3102	0.37	3.45	0.17	0.37	0.35	0.72
	3103	0.30	3.34	0.22	0.34	0.31	0.65
	3104	0.31	3.43	0.19	0.39	0.37	0.76
	3105	0.33	3.20	0.22	0.34	0.36	0.69
	3106	0.30	3.17	0.20	0.34	0.30	0.64
	3107	0.34	3.13	0.17	0.36	0.36	0.72
	3108	0.32	3.49	0.20	0.36	0.34	0.70
	3109	0.33	3.38	0.31	0.36	0.37	0.73
	3110a)	0.32Z	3.55Z	0.16Z	0.34Z	0.34Z	0.68Z
	3111	0.38	3.40	0.21	0.34	0.33	0.67
	3112	0.34	4.07	0.28	0.40	0.40	0.81
	Mean	0.33	3.41	0.22	0.36	0.35	0.72
	S.D.	0.03	0.25	0.04	0.02	0.03	0.06

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 8-25 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 200

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	3101	39	45	84	51.6	71.5	123.1	717
	3102	41	36	77	44.1	50.3	94.4	729
	3103	34	36	70	51.7	51.7	103.4	643
	3104	40	45	85	56.2	61.0	117.2	630
	3105	38	41	79	52.8	44.3	97.1	846
	3106	31	32	63	42.3	42.1	84.4	859
	3107	41	44	85	52.0	46.6	98.6	745
	3108	49	51	100	46.7	46.4	93.1	628
	3109	44	48	92	49.1	40.7	89.8	568
	3110a)	36Z	39Z	75Z	41.3Z	47.3Z	88.6Z	923Z
	3111	35	36	71	41.1	41.2	82.3	555
	3112	48	53	101	69.6	66.3	135.9	852
	Mean	40	42	82	50.7	51.1	101.8	707
	S.D.	6	7	12	7.9	10.6	16.9	111
Relative	3101	11	13	24	14.7	20.4	35.1	204
	3102	13	11	24	14.0	16.0	30.0	231
	3103	10	11	22	15.9	15.9	31.8	198
	3104	12	14	26	17.2	18.7	36.0	193
	3105	11	12	24	15.8	13.2	29.0	253
	3106	10	11	21	14.2	14.2	28.4	289
	3107	12	13	25	15.2	13.6	28.7	217
	3108	16	17	33	15.6	15.5	31.1	210
	3109	14	16	30	16.0	13.3	29.3	186
	3110a)	12Z	13Z	25Z	13.5Z	15.5Z	29.0Z	303Z
	3111	11	12	23	13.4	13.5	26.9	181
	3112	15	17	32	21.8	20.7	42.5	266
	Mean	12	13	26	15.8	15.9	31.7	221
	S.D.	2	2	4	2.3	2.8	4.5	35

a): Non-pregnant
Z: Data was excluded from statistical analysis.

Appendix 8-26 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4101	313	2.04	18.3	11.6	11.9	23.5	276
	4102	307	1.96	19.1	4.9	6.5	11.4	183
	4103	359	2.04	18.5	8.3	7.6	15.9	296
	4104	328	1.95	20.2	8.5	7.1	15.6	307
	4105	349	2.04	23.3	8.3	9.9	18.2	216
	4106	320	2.07	20.2	10.7	9.8	20.5	234
	4107	337	2.06	21.8	10.4	8.6	19.0	196
	4108	340	2.04	18.9	9.3	11.9	21.2	259
	4109	332	2.02	21.4	10.5	8.8	19.3	223
	4110	317	2.06	16.0	6.3	9.6	15.9	255
	4111	320	1.96	19.6	7.9	6.5	14.4	206
	4112	314	1.96	14.9	8.7	7.5	16.2	169
	Mean	328	2.02	19.4	8.8	8.8	17.6	235
	S.D.	16	0.05	2.3	1.9	1.9	3.3	44
Relative	4101		0.65	5.8	3.7	3.8	7.5	88
	4102		0.64	6.2	1.6	2.1	3.7	60
	4103		0.57	5.2	2.3	2.1	4.4	82
	4104		0.59	6.2	2.6	2.2	4.8	94
	4105		0.58	6.7	2.4	2.8	5.2	62
	4106		0.65	6.3	3.3	3.1	6.4	73
	4107		0.61	6.5	3.1	2.6	5.6	58
	4108		0.60	5.6	2.7	3.5	6.2	76
	4109		0.61	6.4	3.2	2.7	5.8	67
	4110		0.65	5.0	2.0	3.0	5.0	80
	4111		0.61	6.1	2.5	2.0	4.5	64
	4112		0.62	4.7	2.8	2.4	5.2	54
	Mean		0.62	5.9	2.7	2.7	5.4	72
	S.D.		0.03	0.6	0.6	0.6	1.0	13

Appendix 8-27 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 1000

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4101	1.25	10.81	0.90	1.32	1.28	2.60
	4102	1.01	11.00	0.93	1.18	1.09	2.27
	4103	1.11	11.06	0.77	1.40	1.44	2.84
	4104	1.01	11.03	0.75	1.12	1.14	2.26
	4105	1.08	11.99	0.73	1.30	1.30	2.60
	4106	1.14	11.85	0.77	1.25	1.24	2.49
	4107	1.11	11.23	0.72	1.33	1.37	2.70
	4108	1.12	12.00	0.77	1.30	1.30	2.60
	4109	1.32	10.80	0.66	1.22	1.17	2.39
	4110	1.05	12.02	0.79	1.15	1.20	2.35
	4111	1.09	11.05	0.66	1.21	1.19	2.40
	4112	1.12	11.15	0.87	1.20	1.20	2.40
	Mean	1.12	11.33	0.78	1.25	1.24	2.49
	S.D.	0.09	0.48	0.09	0.08	0.10	0.18
Relative	4101	0.40	3.45	0.29	0.42	0.41	0.83
	4102	0.33	3.58	0.30	0.38	0.36	0.74
	4103	0.31	3.08	0.21	0.39	0.40	0.79
	4104	0.31	3.36	0.23	0.34	0.35	0.69
	4105	0.31	3.44	0.21	0.37	0.37	0.74
	4106	0.36	3.70	0.24	0.39	0.39	0.78
	4107	0.33	3.33	0.21	0.39	0.41	0.80
	4108	0.33	3.53	0.23	0.38	0.38	0.76
	4109	0.40	3.25	0.20	0.37	0.35	0.72
	4110	0.33	3.79	0.25	0.36	0.38	0.74
	4111	0.34	3.45	0.21	0.38	0.37	0.75
	4112	0.36	3.55	0.28	0.38	0.38	0.76
	Mean	0.34	3.46	0.24	0.38	0.38	0.76
	S.D.	0.03	0.19	0.03	0.02	0.02	0.04

Appendix 8-28 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Main group, End of administration)
Dose (mg/kg): 1000

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4101	41	44	85	42.9	47.4	90.3	648
	4102	41	44	85	68.2	33.9	102.1	751
	4103	39	39	78	43.4	60.9	104.3	883
	4104	36	40	76	55.0	51.6	106.6	823
	4105	42	45	87	61.3	42.6	103.9	638
	4106	42	43	85	64.7	52.9	117.6	635
	4107	48	51	99	49.2	51.8	101.0	745
	4108	41	44	85	49.0	64.0	113.0	554
	4109	38	44	82	49.0	49.1	98.1	724
	4110	39	45	84	52.6	42.0	94.6	601
	4111	36	36	72	54.1	50.1	104.2	644
	4112	39	42	81	45.7	58.0	103.7	721
	Mean	40	43	83	52.9	50.4	103.3	697
	S.D.	3	4	7	8.2	8.4	7.3	95
Relative	4101	13	14	27	13.7	15.1	28.8	207
	4102	13	14	28	22.2	11.0	33.3	245
	4103	11	11	22	12.1	17.0	29.1	246
	4104	11	12	23	16.8	15.7	32.5	251
	4105	12	13	25	17.6	12.2	29.8	183
	4106	13	13	27	20.2	16.5	36.8	198
	4107	14	15	29	14.6	15.4	30.0	221
	4108	12	13	25	14.4	18.8	33.2	163
	4109	11	13	25	14.8	14.8	29.5	218
	4110	12	14	26	16.6	13.2	29.8	190
	4111	11	11	23	16.9	15.7	32.6	201
	4112	12	13	26	14.6	18.5	33.0	230
	Mean	12	13	26	16.2	15.3	31.5	213
	S.D.	1	1	2	2.8	2.3	2.4	27

Appendix 8-29 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1113	296	1.85	19.2	7.0	7.2	14.2	336
	1114	291	2.08	19.3	8.7	7.3	16.0	313
	1115	250	1.90	18.5	7.9	8.3	16.2	194
	1116	289	1.96	17.8	9.0	10.7	19.7	284
	1117	275	1.96	19.9	10.5	10.7	21.2	314
	Mean	280	1.95	18.9	8.6	8.8	17.5	288
	S.D.	19	0.09	0.8	1.3	1.8	2.9	56
Relative	1113		0.63	6.5	2.4	2.4	4.8	114
	1114		0.71	6.6	3.0	2.5	5.5	108
	1115		0.76	7.4	3.2	3.3	6.5	78
	1116		0.68	6.2	3.1	3.7	6.8	98
	1117		0.71	7.2	3.8	3.9	7.7	114
	Mean		0.70	6.8	3.1	3.2	6.3	102
	S.D.		0.05	0.5	0.5	0.7	1.1	15

Appendix 8-30 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1113	0.95	7.75	0.58	0.96	0.98	1.94
	1114	0.90	7.24	0.58	0.98	1.03	2.01
	1115	0.84	6.68	0.45	0.96	0.95	1.91
	1116	0.83	7.58	0.54	0.93	0.97	1.90
	1117	0.99	6.68	0.55	0.90	0.90	1.80
	Mean	0.90	7.19	0.54	0.95	0.97	1.91
	S.D.	0.07	0.50	0.05	0.03	0.05	0.08
Relative	1113	0.32	2.62	0.20	0.32	0.33	0.66
	1114	0.31	2.49	0.20	0.34	0.35	0.69
	1115	0.34	2.67	0.18	0.38	0.38	0.76
	1116	0.29	2.62	0.19	0.32	0.34	0.66
	1117	0.36	2.43	0.20	0.33	0.33	0.65
	Mean	0.32	2.57	0.19	0.34	0.35	0.68
	S.D.	0.03	0.10	0.01	0.02	0.02	0.05

Appendix 8-31 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1113	30	31	61	41.4	38.2	79.6	871
	1114	37	40	77	39.9	49.3	89.2	673
	1115	34	34	68	49.1	42.8	91.9	450
	1116	29	31	60	43.1	40.0	83.1	393
	1117	33	37	70	42.4	50.3	92.7	641
	Mean	33	35	67	43.2	44.1	87.3	606
	S.D.	3	4	7	3.5	5.4	5.7	191
Relative	1113	10	10	21	14.0	12.9	26.9	294
	1114	13	14	26	13.7	16.9	30.7	231
	1115	14	14	27	19.6	17.1	36.8	180
	1116	10	11	21	14.9	13.8	28.8	136
	1117	12	13	25	15.4	18.3	33.7	233
	Mean	12	12	24	15.5	15.8	31.4	215
	S.D.	2	2	3	2.4	2.3	3.9	60

Appendix 8-32 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4113	314	1.96	19.1	9.0	9.6	18.6	550
	4114	280	2.04	21.1	11.4	11.0	22.4	368
	4115	279	2.05	18.9	11.1	11.9	23.0	278
	4116	270	1.97	16.1	8.1	8.0	16.1	350
	4117	284	2.00	16.7	7.7	8.4	16.1	283
	Mean	285	2.00	18.4	9.5	9.8	19.2	366
	S.D.	17	0.04	2.0	1.7	1.7	3.3	110
Relative	4113		0.62	6.1	2.9	3.1	5.9	175
	4114		0.73	7.5	4.1	3.9	8.0	131
	4115		0.73	6.8	4.0	4.3	8.2	100
	4116		0.73	6.0	3.0	3.0	6.0	130
	4117		0.70	5.9	2.7	3.0	5.7	100
	Mean		0.70	6.5	3.3	3.5	6.8	127
	S.D.		0.05	0.7	0.7	0.6	1.2	31

Appendix 8-33 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4113	0.94	8.43	0.69	1.14	1.07	2.21
	4114	0.92	7.62	0.55	1.12	1.11	2.23
	4115	0.86	7.38	0.47	0.97	0.93	1.90
	4116	0.92	7.84	0.54	0.99	1.03	2.02
	4117	0.96	7.61	0.56	1.26	1.15	2.41
	Mean	0.92	7.78	0.56	1.10	1.06	2.15
	S.D.	0.04	0.40	0.08	0.12	0.08	0.20
Relative	4113	0.30	2.68	0.22	0.36	0.34	0.70
	4114	0.33	2.72	0.20	0.40	0.40	0.80
	4115	0.31	2.65	0.17	0.35	0.33	0.68
	4116	0.34	2.90	0.20	0.37	0.38	0.75
	4117	0.34	2.68	0.20	0.44	0.40	0.85
	Mean	0.32	2.73	0.20	0.38	0.37	0.76
	S.D.	0.02	0.10	0.02	0.04	0.03	0.07

Appendix 8-34 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (Satellite group, End of administration)
Dose (mg/kg): 1000

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4113	34	38	72	54.7	52.0	106.7	827
	4114	37	39	76	54.4	50.6	105.0	656
	4115	31	30	61	47.3	44.6	91.9	713
	4116	31	37	68	42.4	42.8	85.2	562
	4117	34	37	71	51.8	47.4	99.2	770
	Mean	33	36	70	50.1	47.5	97.6	706
	S.D.	3	4	6	5.2	3.9	9.0	102
Relative	4113	11	12	23	17.4	16.6	34.0	263
	4114	13	14	27	19.4	18.1	37.5	234
	4115	11	11	22	17.0	16.0	32.9	256
	4116	11	14	25	15.7	15.9	31.6	208
	4117	12	13	25	18.2	16.7	34.9	271
	Mean	12	13	24	17.5	16.7	34.2	246
	S.D.	1	1	2	1.4	0.9	2.2	26

Appendix 8-35 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1008	495	2.26	13.1	11.6	13.4	25.0	214
	1009	471	2.07	14.4	12.0	9.0	21.0	176
	1010	474	2.08	12.0	9.7	9.3	19.0	240
	1011	549	2.15	15.7	12.8	18.9	31.7	131
	1012	483	2.05	11.4	12.3	10.2	22.5	266
	Mean	494	2.12	13.3	11.7	12.2	23.8	205
	S.D.	32	0.09	1.8	1.2	4.2	4.9	53
Relative	1008		0.46	2.6	2.3	2.7	5.1	43
	1009		0.44	3.1	2.5	1.9	4.5	37
	1010		0.44	2.5	2.0	2.0	4.0	51
	1011		0.39	2.9	2.3	3.4	5.8	24
	1012		0.42	2.4	2.5	2.1	4.7	55
	Mean		0.43	2.7	2.3	2.4	4.8	42
	S.D.		0.03	0.3	0.2	0.6	0.7	12

Appendix 8-36 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1008	1.54	11.55	0.75	1.62	1.65	3.27
	1009	1.41	11.74	0.70	1.65	1.69	3.34
	1010	1.44	13.01	0.67	1.68	1.61	3.29
	1011	1.72	14.04	0.69	1.88	1.96	3.84
	1012	1.57	11.86	0.71	1.69	1.71	3.40
	Mean	1.54	12.44	0.70	1.70	1.72	3.43
	S.D.	0.12	1.06	0.03	0.10	0.14	0.24
Relative	1008	0.31	2.33	0.15	0.33	0.33	0.66
	1009	0.30	2.49	0.15	0.35	0.36	0.71
	1010	0.30	2.74	0.14	0.35	0.34	0.69
	1011	0.31	2.56	0.13	0.34	0.36	0.70
	1012	0.33	2.46	0.15	0.35	0.35	0.70
	Mean	0.31	2.52	0.14	0.34	0.35	0.69
	S.D.	0.01	0.15	0.01	0.01	0.01	0.02

Appendix 8-37 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	1008	29	34	63	1.69	1.73	3.42
	1009	30	32	62	1.46	1.47	2.93
	1010	32	35	67	1.41	1.38	2.79
	1011	27	30	57	1.71	1.70	3.41
	1012	27	28	55	1.37	1.35	2.72
	Mean	29	32	61	1.53	1.53	3.05
	S.D.	2	3	5	0.16	0.18	0.34
Relative	1008	6	7	13	0.34	0.35	0.69
	1009	6	7	13	0.31	0.31	0.62
	1010	7	7	14	0.30	0.29	0.59
	1011	5	5	10	0.31	0.31	0.62
	1012	6	6	11	0.28	0.28	0.56
	Mean	6	6	12	0.31	0.31	0.62
	S.D.	1	1	2	0.02	0.03	0.05

Appendix 8-38 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	1008	700	713	1413	1.73	1.78
	1009	618	589	1207	1.69	1.57
	1010	698	658	1356	1.15	1.32
	1011	677	675	1352	1.85	1.38
	1012	577	565	1142	1.66	1.15
	Mean	654	640	1294	1.62	1.44
	S.D.	54	61	114	0.27	0.24
Relative	1008	141	144	285	0.35	0.36
	1009	131	125	256	0.36	0.33
	1010	147	139	286	0.24	0.28
	1011	123	123	246	0.34	0.25
	1012	119	117	236	0.34	0.24
	Mean	132	130	262	0.33	0.29
	S.D.	12	11	23	0.05	0.05

Appendix 8-39 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4008	519	2.12	14.3	12.9	10.4	23.3	224
	4009	469	2.07	14.0	14.7	11.7	26.4	161
	4010	597	2.30	18.2	19.0	21.6	40.6	384
	4011	474	2.18	11.9	12.4	9.9	22.3	263
	4012	448	2.09	12.6	12.5	14.0	26.5	253
	Mean	501	2.15	14.2	14.3	13.5	27.8	257
	S.D.	59	0.09	2.4	2.8	4.8	7.4	81
Relative	4008		0.41	2.8	2.5	2.0	4.5	43
	4009		0.44	3.0	3.1	2.5	5.6	34
	4010		0.39	3.0	3.2	3.6	6.8	64
	4011		0.46	2.5	2.6	2.1	4.7	55
	4012		0.47	2.8	2.8	3.1	5.9	56
	Mean		0.43	2.8	2.8	2.7	5.5	50
	S.D.		0.03	0.2	0.3	0.7	0.9	12

Appendix 8-40 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4008	1.50	13.18	0.69	1.90	1.90	3.80
	4009	1.39	11.47	0.67	1.64	1.74	3.38
	4010	1.73	16.20	0.89	2.17	2.38	4.55
	4011	1.37	11.25	0.62	1.55	1.59	3.14
	4012	1.36	11.04	0.55	1.72	1.76	3.48
	Mean	1.47	12.63	0.68	1.80	1.87	3.67
	S.D.	0.16	2.17	0.13	0.25	0.30	0.55
Relative	4008	0.29	2.54	0.13	0.37	0.37	0.73
	4009	0.30	2.45	0.14	0.35	0.37	0.72
	4010	0.29	2.71	0.15	0.36	0.40	0.76
	4011	0.29	2.37	0.13	0.33	0.34	0.66
	4012	0.30	2.46	0.12	0.38	0.39	0.78
	Mean	0.29	2.51	0.13	0.36	0.37	0.73
	S.D.	0.01	0.13	0.01	0.02	0.02	0.05

Appendix 8-41 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Testis (R) g(g/100g BW)	Testis (L) g(g/100g BW)	Testis (R+L) g(g/100g BW)
Absolute	4008	31	36	67	1.62	1.64	3.26
	4009	30	30	60	1.75	1.78	3.53
	4010	36	36	72	1.99	2.01	4.00
	4011	24	30	54	1.53	1.55	3.08
	4012	27	24	51	1.66	1.69	3.35
	Mean	30	31	61	1.71	1.73	3.44
	S.D.	5	5	9	0.18	0.18	0.35
Relative	4008	6	7	13	0.31	0.32	0.63
	4009	6	6	13	0.37	0.38	0.75
	4010	6	6	12	0.33	0.34	0.67
	4011	5	6	11	0.32	0.33	0.65
	4012	6	5	11	0.37	0.38	0.75
	Mean	6	6	12	0.34	0.35	0.69
	S.D.	0	1	1	0.03	0.03	0.06

Appendix 8-42 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of male rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Epididymis (R) mg(mg/100g BW)	Epididymis (L) mg(mg/100g BW)	Epididymis (R+L) mg(mg/100g BW)	Seminal vesicle g(g/100g BW)	Prostate g(g/100g BW)
Absolute	4008	715	725	1440	1.90	1.25
	4009	661	692	1353	1.73	1.17
	4010	799	876	1675	1.85	1.42
	4011	624	603	1227	1.40	0.95
	4012	666	737	1403	1.70	1.31
	Mean	693	727	1420	1.72	1.22
	S.D.	68	99	164	0.20	0.18
Relative	4008	138	140	277	0.37	0.24
	4009	141	148	288	0.37	0.25
	4010	134	147	281	0.31	0.24
	4011	132	127	259	0.30	0.20
	4012	149	165	313	0.38	0.29
	Mean	139	145	284	0.35	0.24
	S.D.	7	14	20	0.04	0.03

Appendix 8-43 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	1118	292	1.96	19.6	10.0	6.9	16.9	266
	1119	286	1.93	18.5	7.3	7.8	15.1	359
	1120	308	2.05	19.1	11.4	8.4	19.8	281
	1121	277	1.96	16.5	6.4	6.6	13.0	295
	1122	287	1.92	17.6	6.3	5.9	12.2	270
	Mean	290	1.96	18.3	8.3	7.1	15.4	294
	S.D.	11	0.05	1.2	2.3	1.0	3.1	38
Relative	1118		0.67	6.7	3.4	2.4	5.8	91
	1119		0.67	6.5	2.6	2.7	5.3	126
	1120		0.67	6.2	3.7	2.7	6.4	91
	1121		0.71	6.0	2.3	2.4	4.7	106
	1122		0.67	6.1	2.2	2.1	4.3	94
	Mean		0.68	6.3	2.8	2.5	5.3	102
	S.D.		0.02	0.3	0.7	0.3	0.8	15

Appendix 8-44 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	1118	0.96	7.05	0.47	0.96	0.94	1.90
	1119	0.96	7.05	0.67	0.96	1.03	1.99
	1120	0.97	8.18	0.55	1.03	1.00	2.03
	1121	0.84	6.93	0.48	0.93	0.94	1.87
	1122	0.88	7.64	0.50	1.04	0.99	2.03
	Mean	0.92	7.37	0.53	0.98	0.98	1.96
	S.D.	0.06	0.53	0.08	0.05	0.04	0.07
Relative	1118	0.33	2.41	0.16	0.33	0.32	0.65
	1119	0.34	2.47	0.23	0.34	0.36	0.70
	1120	0.31	2.66	0.18	0.33	0.32	0.66
	1121	0.30	2.50	0.17	0.34	0.34	0.68
	1122	0.31	2.66	0.17	0.36	0.34	0.71
	Mean	0.32	2.54	0.18	0.34	0.34	0.68
	S.D.	0.02	0.11	0.03	0.01	0.02	0.03

Appendix 8-45 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 0

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	1118	25	33	58	40.6	42.4	83.0	419
	1119	26	26	52	38.1	42.9	81.0	576
	1120	28	33	61	54.3	50.5	104.8	729
	1121	34	36	70	53.2	37.1	90.3	501
	1122	29	33	62	46.8	49.8	96.6	568
	Mean	28	32	61	46.6	44.5	91.1	559
	S.D.	4	4	7	7.3	5.6	9.8	114
Relative	1118	9	11	20	13.9	14.5	28.4	143
	1119	9	9	18	13.3	15.0	28.3	201
	1120	9	11	20	17.6	16.4	34.0	237
	1121	12	13	25	19.2	13.4	32.6	181
	1122	10	11	22	16.3	17.4	33.7	198
	Mean	10	11	21	16.1	15.3	31.4	192
	S.D.	1	1	3	2.5	1.6	2.8	34

Appendix 8-46 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Body weight g	Brain g(g/100g BW)	Pituitary mg(mg/100g BW)	Thyroid (R) mg(mg/100g BW)	Thyroid (L) mg(mg/100g BW)	Thyroid (R+L) mg(mg/100g BW)	Thymus mg(mg/100g BW)
Absolute	4118	273	1.95	17.1	5.0	6.6	11.6	380
	4119	280	2.11	17.1	10.6	8.4	19.0	245
	4120	289	1.93	13.1	9.3	6.8	16.1	284
	4121	295	1.92	18.2	9.0	8.5	17.5	194
	4122	325	2.04	18.2	7.9	4.6	12.5	284
	Mean	292	1.99	16.7	8.4	7.0	15.3	277
	S.D.	20	0.08	2.1	2.1	1.6	3.2	68
Relative	4118		0.71	6.3	1.8	2.4	4.2	139
	4119		0.75	6.1	3.8	3.0	6.8	88
	4120		0.67	4.5	3.2	2.4	5.6	98
	4121		0.65	6.2	3.1	2.9	5.9	66
	4122		0.63	5.6	2.4	1.4	3.8	87
	Mean		0.68	5.7	2.9	2.4	5.3	96
	S.D.		0.05	0.7	0.8	0.6	1.2	27

Appendix 8-47 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Heart g(g/100g BW)	Liver g(g/100g BW)	Spleen g(g/100g BW)	Kidney (R) g(g/100g BW)	Kidney (L) g(g/100g BW)	Kidney (R+L) g(g/100g BW)
Absolute	4118	0.95	6.82	0.44	0.97	0.98	1.95
	4119	0.94	7.12	0.64	0.96	0.91	1.87
	4120	0.88	7.16	0.50	1.00	1.02	2.02
	4121	0.96	7.87	0.51	1.15	1.20	2.35
	4122	1.04	9.29	0.77	1.05	1.04	2.09
	Mean	0.95	7.65	0.57	1.03	1.03	2.06
	S.D.	0.06	0.99	0.13	0.08	0.11	0.18
Relative	4118	0.35	2.50	0.16	0.36	0.36	0.71
	4119	0.34	2.54	0.23	0.34	0.33	0.67
	4120	0.30	2.48	0.17	0.35	0.35	0.70
	4121	0.33	2.67	0.17	0.39	0.41	0.80
	4122	0.32	2.86	0.24	0.32	0.32	0.64
	Mean	0.33	2.61	0.19	0.35	0.35	0.70
	S.D.	0.02	0.16	0.04	0.03	0.04	0.06

Appendix 8-48 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual organ weight of female rats (End of recovery)
Dose (mg/kg): 1000

	Animal number	Adrenal (R) mg(mg/100g BW)	Adrenal (L) mg(mg/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Ovary (R) mg(mg/100g BW)	Ovary (L) mg(mg/100g BW)	Ovary (R+L) mg(mg/100g BW)	Uterus mg(mg/100g BW)
Absolute	4118	27	28	55	41.0	52.5	93.5	740
	4119	29	31	60	47.7	32.4	80.1	500
	4120	25	28	53	67.4	68.6	136.0	443
	4121	30	32	62	36.6	35.1	71.7	622
	4122	37	43	80	71.8	54.2	126.0	810
	Mean	30	32	62	52.9	48.6	101.5	623
	S.D.	5	6	11	15.8	14.9	28.3	155
Relative	4118	10	10	20	15.0	19.2	34.2	271
	4119	10	11	21	17.0	11.6	28.6	179
	4120	9	10	18	23.3	23.7	47.1	153
	4121	10	11	21	12.4	11.9	24.3	211
	4122	11	13	25	22.1	16.7	38.8	249
	Mean	10	11	21	18.0	16.6	34.6	213
	S.D.	1	1	3	4.6	5.1	8.9	49

Appendix 9-1(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1001 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney(alpha2u globulin)	Alpha2u globulin IHC:positive
Kidney(PAS stain)	PAS reaction negative
Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-2(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1002 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Heart	Cell infiltration,interstitial: minimal, focal
Testis	Atrophy,seminiferous tubular: minimal, unilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Spleen, Stomach, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 9-3(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1003 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-4(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1004 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Testis	Atrophy,seminiferous tubular: minimal, bilateral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Sciatic nerve, Spleen, Stomach, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder

Appendix 9-5(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1005 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis
Stomach	Erosion: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-6(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1006 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-7(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1007 Male 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-8(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1008 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-9(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1009 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-10(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1010 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-11(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1011 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-12(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1012 Male 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-13(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2001 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-14(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2002 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-15(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2003 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-16(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2004 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-17(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2005 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-18(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2006 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-19(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2007 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-20(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2008 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-21(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2009 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Pancreas	Fibrosis,islet: mild
Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-22(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2010 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-23(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2011 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-24(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2012 Male 40 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus)
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Seminal vesicle(coagulating gland)
Spinal cord,thoracic, Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-25(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3001 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney(alpha2u globulin)	Alpha2u globulin IHC:positive
Kidney	Increased eosinophilic body,tubular: minimal
Kidney(PAS stain)	PAS reaction negative

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-26(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3002 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-27(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3003 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach
Urinary bladder

Appendix 9-28(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3004 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney	Increased eosinophilic body,tubular: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-29(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3005 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney	Increased eosinophilic body,tubular: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-30(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3006 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-31(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3007 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-32(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3008 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-33(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3009 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-34(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3010 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-35(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3011 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-36(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3012 Male 200 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-37(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4001 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Kidney(alpha2u globulin)	Alpha2u globulin IHC:positive
Kidney	Increased eosinophilic body,tubular: mild, bilateral No finding correlating with necropsy data
Kidney(PAS stain)	PAS reaction negative
Pancreas	Atrophy,acinar: minimal, focal
Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Parathyroid, Pituitary, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-38(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4002 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Kidney	Discoloration,black,bilateral
Lung(bronchus)	Focus,black: 1 present 7x7mm
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Intestine,colon	Hyperplasia,mucosal,diffuse: minimal
Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Kidney	Increased eosinophilic body,tubular: mild, bilateral No finding correlating with necropsy data
Lung(bronchus)	Cell infiltration: mild inflammatory cell,black pigment-laden macrophage,with thickening alveolar wall
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Lymph node,mesenteric, Lymph node,submandibular, Liver, Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-39(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4003 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

Stomach	Thickening,limiting ridge: mild
Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

Epididymis	Cell debris,lumen: minimal, bilateral
Heart	Cell infiltration,interstitial: minimal, focal
Intestine,ileum(Peyer's patch)	Cell infiltration,mucosal: mild, focal neutrophilic
Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Liver	Cell infiltration,centrilobular: minimal, mononuclear mononuclear
Prostate	Cell infiltration,interstitial: minimal, lymphocytic ventral and dorsolateral
Spleen	Hematopoiesis,extramedullary: mild erythropoiesis
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild
Testis	Atrophy,seminiferous tubular: mild, bilateral No finding correlating with necropsy data

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,colon, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Lung(bronchus), Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Thymus, Trachea, Thyroid, Urinary bladder

Appendix 9-40(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4004 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Heart	Cell infiltration,interstitial: minimal, focal
Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Intestine,colon	Hyperplasia,mucosal,diffuse: minimal
Kidney	Increased eosinophilic body,tubular: mild, bilateral No finding correlating with necropsy data
Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Stomach	Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,rectum, Lymph node,mesenteric, Lymph node,submandibular, Liver
Parathyroid, Pancreas, Pituitary, Prostate, Salivary gland,submandibular
Skin,inguinal, Sciatic nerve, Spleen, Skeletal muscle,femoral
Seminal vesicle(coagulating gland), Spinal cord,thoracic, Testis, Thymus, Trachea
Thyroid, Urinary bladder

Appendix 9-41(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4005 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Intestine,colon	Hyperplasia,mucosal,diffuse: minimal
Kidney	Increased eosinophilic body,tubular: mild
Stomach	Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: mild
Urinary bladder	Hyperplasia,transitional,diffuse: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Epididymis, Eye
Heart, Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,rectum, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Parathyroid, Pancreas
Pituitary, Prostate, Salivary gland,submandibular, Sciatic nerve, Spleen
Skeletal muscle,femoral, Seminal vesicle(coagulating gland), Spinal cord,thoracic
Testis, Thymus, Trachea, Thyroid

Appendix 9-42(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4006 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-43(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4007 Male 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-44(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4008 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Stomach	Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Urinary bladder

Appendix 9-45(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4009 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Kidney	Increased eosinophilic body,tubular: minimal
Urinary bladder	Hyperplasia,transitional,diffuse: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach

Appendix 9-46(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4010 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach, Testis
Urinary bladder

Appendix 9-47(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4011 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

Stomach	Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Testis
Urinary bladder

Appendix 9-48(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4012 Male 1000 mg/kg Day 57 End of recovery period

Gross pathology:

Testis	Discoloration,blue,bilateral
Other tissues	Not remarkable

Histopathology:

Testis	Atrophy,seminiferous tubular: minimal, bilateral No findings correlating with necropsy data
Urinary bladder	Hyperplasia,transitional,diffuse: mild

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Stomach

Appendix 9-49(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1101 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-50(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1102 Female 0 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Eye	Dysplasia,retinal: mild
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-51(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1103 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-52(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1104 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-53(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1105 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-54(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1106 Female 0 mg/kg Day 48 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-55(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1107 Female 0 mg/kg Day 40 All littermates died

Gross pathology:

Uterus	Prolapse Thickening,wall,horn,unilateral: the region of prolapse of the uterus,left
Other tissues	Not remarkable

Histopathology:

Bone+Bone marrow,femoral	Hematopoiesis,increased: mild
Ovary	Atrophy: mild, unilateral
Salivary gland,submandibular	Hypertrophy,acinar cell: mild
Spleen	Hematopoiesis,extramedullary: mild granulopoiesis and erythropoiesis
Thymus	Atrophy: minimal
Uterus	Inflammation: mild with edema of muscle layer and proliferation of vessel

Following tissues : Not remarkable

Adrenal, Cerebellum(Pons), Cerebrum, Eye, Heart, Intestine,duodenum
Intestine,jejunum, Intestine,ileum(Peyer's patch), Intestine,cecum
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Parathyroid, Pancreas
Pituitary, Sciatic nerve, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic
Trachea, Thyroid, Urinary bladder, Vagina

Appendix 9-56(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1108 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-57(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1109 Female 0 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 2 present 2x2,1x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-58(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1110 Female 0 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-59(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1111 Female 0 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-60(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1112 Female 0 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-61(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1113 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-62(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1114 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-63(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1115 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Stomach	Bulla formation,limiting ridge: minimal with edema squamous cell and inflammatory cell infiltration

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-64(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1116 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Lung(bronchus)	Cell infiltration: minimal inflammatory cell
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Ovary, Parathyroid
Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve, Stomach
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-65(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1117 Female 0 mg/kg Day 43 End of administration period (D42)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-66(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1118 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-67(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1119 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-68(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1120 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Stomach	Erosion: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Urinary bladder

Appendix 9-69(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1121 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-70(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 1122 Female 0 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-71(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2101 Female 40 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-72(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2102 Female 40 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-73(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2103 Female 40 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-74(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2104 Female 40 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-75(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2105 Female 40 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-76(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2106 Female 40 mg/kg Day 46 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 2 present 1x1mm
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-77(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2107 Female 40 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-78(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2108 Female 40 mg/kg Day 42 End of administration period (L4)

Gross pathology:

Lung(bronchus)	Focus,dark red: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-79(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2109 Female 40 mg/kg Day 41 Undelivered

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-80(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2110 Female 40 mg/kg Day 43 Undelivered

Gross pathology:

All tissues	Not remarkable

Histopathology:

Heart	Cell infiltration,interstitial: minimal, focal
Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-81(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2111 Female 40 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-82(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 2112 Female 40 mg/kg Day 54 Undelivered

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-83(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3101 Female 200 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-84(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3102 Female 200 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-85(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3103 Female 200 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-86(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3104 Female 200 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-87(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3105 Female 200 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-88(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3106 Female 200 mg/kg Day 42 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-89(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3107 Female 200 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-90(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3108 Female 200 mg/kg Day 44 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-91(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3109 Female 200 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-92(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3110 Female 200 mg/kg Day 41 Undelivered

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Spleen, Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea
Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-93(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3111 Female 200 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues Not remarkable

Histopathology:

No tissues examined

Appendix 9-94(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 3112 Female 200 mg/kg Day 45 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-95(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4101 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Stomach, Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-96(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4102 Female 1000 mg/kg Day 48 End of administration period (L4)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-97(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4103 Female 1000 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-98(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4104 Female 1000 mg/kg Day 42 End of administration period (L4)

Gross pathology:

Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: minimal erythropoiesis
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-99(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4105 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 2 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Spleen	Hematopoiesis,extramedullary: mild erythropoiesis
Stomach	Erosion: minimal Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Sciatic nerve, Skeletal muscle,femoral
Spinal cord,thoracic, Thymus, Trachea, Thyroid, Urinary bladder, Uterus, Vagina

Appendix 9-100(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4106 Female 1000 mg/kg Day 44 End of administration period (L4)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-101(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4107 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis
Stomach	Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: minimal
Urinary bladder	Hyperplasia,transitional,diffuse: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Uterus
Vagina

Appendix 9-102(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4108 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Stomach	Focus,dark red,glandular stomach: 1 present 1x1mm
Other tissues	Not remarkable

Histopathology:

Spleen	Hematopoiesis,extramedullary: mild erythropoiesis
Stomach	Erosion: minimal Arteritis: minimal Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney
Lymph node,mesenteric, Lymph node,submandibular, Liver, Lung(bronchus), Ovary
Parathyroid, Pancreas, Pituitary, Salivary gland,submandibular, Sciatic nerve
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-103(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4109 Female 1000 mg/kg Day 44 End of administration period (L4)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Stomach	Thickening,limiting ridge: mild
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-104(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4110 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-105(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4111 Female 1000 mg/kg Day 43 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-106(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4112 Female 1000 mg/kg Day 46 End of administration period (L4)

Gross pathology:

All tissues	Not remarkable

Histopathology:

No tissues examined

Appendix 9-107(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4113 Female 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Lung(bronchus)	Aggregation,alveolar macrophage: minimal
Stomach	Hyperplasia,squamous,limiting ridge: mild
Urinary bladder	Hyperplasia,transitional,diffuse: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Uterus
Vagina

Appendix 9-108(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4114 Female 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Pituitary	Cyst: mild
Stomach	Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: mild
Urinary bladder	Hyperplasia,transitional,diffuse: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Uterus
Vagina

Appendix 9-109(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4115 Female 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild
Urinary bladder	Hyperplasia,transitional,diffuse: minimal

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Intestine,rectum, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid, Uterus
Vagina

Appendix 9-110(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4116 Female 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Stomach	Hyperplasia,mucosal,glandular stomach: mild Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,cecum, Intestine,colon, Kidney, Lymph node,mesenteric
Lymph node,submandibular, Liver, Lung(bronchus), Ovary, Parathyroid, Pancreas
Pituitary, Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-111(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4117 Female 1000 mg/kg Day 43 End of administration period (D42)

Gross pathology:

General descriptions	Discoloration,blue,subcutaneous,systemic
Kidney	Discoloration,black,bilateral
Other tissues	Not remarkable

Histopathology:

Intestine,cecum	Hyperplasia,mucosal,diffuse: minimal
Intestine,rectum	Hyperplasia,mucosal,diffuse: minimal
Stomach	Hyperplasia,mucosal,glandular stomach: minimal Hyperplasia,squamous,limiting ridge: mild

Following tissues : Not remarkable

Adrenal, Bone+Bone marrow,femoral, Cerebellum(Pons), Cerebrum, Eye, Heart
Intestine,duodenum, Intestine,jejunum, Intestine,ileum(Peyer's patch)
Intestine,colon, Kidney, Lymph node,mesenteric, Lymph node,submandibular, Liver
Lung(bronchus), Ovary, Parathyroid, Pancreas, Pituitary
Salivary gland,submandibular, Skin,inguinal, Sciatic nerve, Spleen
Skeletal muscle,femoral, Spinal cord,thoracic, Thymus, Trachea, Thyroid
Urinary bladder, Uterus, Vagina

Appendix 9-112(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4118 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Urinary bladder	Hyperplasia,transitional,diffuse: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach

Appendix 9-113(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4119 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues Not remarkable

Histopathology:

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-114(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4120 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

All tissues	Not remarkable

Histopathology:

Intestine,cecum	Cell infiltration,mucosal: minimal, lymphocytic

Following tissues : Not remarkable

Intestine,colon, Intestine,rectum, Stomach, Urinary bladder

Appendix 9-115(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4121 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

Tissue around the urethral orifice	Swelling
Urinary bladder	Thickening,wall: moderate Calculus: many 3x3x2-6x6x6mm
Other tissues	Not remarkable

Histopathology:

Tissue around the urethral orifice	Inflammation: mild Basophilic materials,urethral lumina: minimal Hyperplasia,squamous,urethra,diffuse: mild squamous metaplasia
Urinary bladder	Cell infiltration,submucosal: mild mononuclear cell Basophilic materials,lumina: minimal PAPILLOMA,transitional cell: 1 present with inflammatory cell infiltration

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Stomach

Appendix 9-116(1/1) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats

Individual gross and histopathological findings

Animal No. 4122 Female 1000 mg/kg Day 57 End of recovery period

Gross pathology:

Kidney	Discoloration,black,bilateral
Liver	Discoloration,black
Other tissues	Not remarkable

Histopathology:

Liver	Erythrophagia,Kupffer cell: mild with pigmentation
Stomach	Hyperplasia,squamous,limiting ridge: minimal

Following tissues : Not remarkable

Intestine,cecum, Intestine,colon, Intestine,rectum, Kidney, Urinary bladder

Appendix 10-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 0

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
1101	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1102	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
1103	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1104	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
1105	E	M	D	P	E	E	M	D	P	E	M	D	D	P	E	4	4.7	
1106	D	P	E	M	D	D	P	E	M	D	D	P	E	M	D	3	5.0	
1107	D	P	E	M	D	P	E	E	M	D	P	E	M	D	P	3	4.5	
1108	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
1109	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
1110	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
1111	D	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
1112	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
Total(%)b)																		0/12(0.0)
Mean																3.7	4.2	
S.D.																0.5	0.3	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100

Appendix 10-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 40

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
2101	D	P	E	M	D	P	E	M	D	P	E	E	M	D	P	3	4.0	
2102	E	E	M	D	P	E	E	M	D	P	E	M	D	D	P	3	5.0	
2103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
2104	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
2105	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
2106	E	M	D	P	E	E	M	D	P	E	E	M	D	P	E	4	4.7	
2107	P	E	M	D	D	P	E	M	D	P	E	M	D	P	E	4	4.3	
2108	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
2109	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
2110c)	D	P	E	M	D	D	P	E	E	M	D	D	P	E	M	3	5.5	
2111	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
2112	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
Total(%)b)																		1/12(8.3)
Mean																3.6	4.3	
S.D.																0.5	0.5	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
c): Abnormal estrous cycle

Appendix 10-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 200

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
3101	D	D	P	E	M	D	P	E	M	D	D	P	E	M	D	3	4.5	
3102	M	D	P	E	M	D	P	E	M	D	P	E	M	D	D	3	4.0	
3103	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
3104	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3105	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3106	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
3107	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3108	D	D	P	E	M	D	P	E	M	D	P	E	E	M	D	3	4.0	
3109c)	M	D	P	E	E	M	D	D	P	E	E	M	D	D	P	2	6.0	
3110	P	E	M	D	P	E	M	D	P	E	M	D	P	E	M	4	4.0	
3111	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
3112	D	D	P	E	E	M	D	P	E	E	M	D	P	E	E	3	5.0	
Total(%)b)																		1/12(8.3)
Mean																3.3	4.3	
S.D.																0.6	0.6	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100
c): Abnormal estrous cycle

Appendix 10-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual estrous cycle in female rats during the pre-mating period (Main group)
Dose (mg/kg): 1000

Animal number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)	Count of estrus	Mean duration of cycles	Index of animals with abnormal estrous cycle (%)
4101	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4102	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4103	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
4104	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4105	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4106	P	E	E	M	D	P	E	E	M	D	P	E	E	M	D	3	5.0	
4107	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4108	M	D	P	E	M	D	P	E	M	D	P	E	M	D	P	3	4.0	
4109	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4110	E	M	D	P	E	M	D	P	E	M	D	P	E	M	D	4	4.0	
4111	P	E	M	D	D	P	E	M	D	P	E	E	M	D	P	3	4.5	
4112	D	P	E	M	D	P	E	M	D	P	E	M	D	P	E	4	4.0	
Total(%)b)																		0/12(0.0)
Mean																3.4	4.1	
S.D.																0.5	0.3	

P: Proestrus E: Estrus M: Metestrus D: Diestrus
a): Day of sampling
b): (No. of animals with abnormal estrous cycle / No. of animals examined)×100

Appendix 11-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 0

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
1001	1101	C	3	P
1002	1102	C	1	P
1003	1103	C	3	P
1004	1104	C	2	P
1005	1105	C	1	P
1006	1106	C	6	P
1007	1107	C	1	P
1008	1108	C	3	P
1009	1109	C	4	P
1010	1110	C	4	P
1011	1111	C	1	P
1012	1112	C	2	P

C: Copulated P: Pregnant

Appendix 11-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 40

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
2001	2101	C	1	P
2002	2102	C	2	P
2003	2103	C	4	P
2004	2104	C	2	P
2005	2105	C	1	P
2006	2106	C	4	P
2007	2107	C	4	P
2008	2108	C	1	P
2009	2109	C	1	NP
2010	2110	C	3	NP
2011	2111	C	2	P
2012	2112	NC	-	-

C: Copulated NC: Not copulated P: Pregnant NP: Non-pregnant

Appendix 11-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 200

Pairing number Male	Female	Copulated or not copulated	Days until copulation	Pregnant or non-pregnant
3001	3101	C	3	P
3002	3102	C	2	P
3003	3103	C	2	P
3004	3104	C	1	P
3005	3105	C	1	P
3006	3106	C	1	P
3007	3107	C	3	P
3008	3108	C	2	P
3009	3109	C	1	P
3010	3110	C	1	NP
3011	3111	C	4	P
3012	3112	C	4	P

C: Copulated P: Pregnant NP: Non-pregnant

Appendix 11-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual mating and fertility of animals
Dose (mg/kg): 1000

Pairing number		Copulated or	Days until	Pregnant or
Male	Female	not copulated	copulation	non-pregnant
4001	4101	C	1	P
4002	4102	C	6	P
4003	4103	C	4	P
4004	4104	C	1	P
4005	4105	C	1	P
4006	4106	C	2	P
4007	4107	C	1	P
4008	4108	C	1	P
4009	4109	C	2	P
4010	4110	C	2	P
4011	4111	C	1	P
4012	4112	C	4	P

C: Copulated P: Pregnant

Appendix 12-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual delivery data on dams
Dose (mg/kg): 0

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
1101	22	15	15	100.0	100.0	0(0.0)	15	0(0.0)
1102	21	14	13	92.9	100.0	0(0.0)	13	0(0.0)
1103	22	15	10	66.7	100.0	0(0.0)	10	0(0.0)
1104	22	15	14	93.3	100.0	0(0.0)	14	0(0.0)
1105	22	14	14	100.0	71.4	0(0.0)	10	0(0.0)
1106	22	16	16	100.0	81.3	0(0.0)	13	0(0.0)
1107	24	4	1	25.0	100.0	1(100.0)	0	0(0.0)
1108	22	14	14	100.0	78.6	0(0.0)	11	0(0.0)
1109	22	17	17	100.0	100.0	0(0.0)	17	0(0.0)
1110	21	16	14	87.5	92.9	0(0.0)	13	0(0.0)
1111	23	16	15	93.8	93.3	0(0.0)	14	0(0.0)
1112	21	15	15	100.0	100.0	0(0.0)	15	0(0.0)
Total		171	158			1	145	0
Mean	22.0	14.3	13.2	88.3	93.1	(8.3)	12.1	(0.0)
S.D.	0.9	3.4	4.2	22.1	10.2	(28.9)	4.3	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 12-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual delivery data on dams
Dose (mg/kg): 40

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
2101	22	18	18	100.0	88.9	0(0.0)	16	0(0.0)
2102	22	18	18	100.0	77.8	0(0.0)	14	0(0.0)
2103	22	17	17	100.0	100.0	0(0.0)	17	0(0.0)
2104	22	17	16	94.1	43.8	0(0.0)	7	0(0.0)
2105	22	13	12	92.3	100.0	0(0.0)	12	0(0.0)
2106	22	17	16	94.1	100.0	0(0.0)	16	0(0.0)
2107	22	16	16	100.0	93.8	1(6.7)	14	0(0.0)
2108	21	16	16	100.0	100.0	0(0.0)	16	0(0.0)
2109	Non-pregnant							
2110	Non-pregnant							
2111	22	16	16	100.0	100.0	0(0.0)	16	0(0.0)
2112	Not copulated							
Total		148	145			1	128	0
Mean	21.9	16.4	16.1	97.8	89.4	(0.7)	14.2	(0.0)
S.D.	0.3	1.5	1.8	3.3	18.7	(2.2)	3.1	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 12-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual delivery data on dams
Dose (mg/kg): 200

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
3101	22	18	18	100.0	100.0	0(0.0)	18	0(0.0)
3102	22	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3103	22	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3104	22	17	17	100.0	88.2	0(0.0)	15	0(0.0)
3105	21	16	16	100.0	93.8	0(0.0)	15	0(0.0)
3106	21	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3107	22	15	15	100.0	80.0	1(8.3)	11	0(0.0)
3108	22	17	17	100.0	94.1	0(0.0)	16	0(0.0)
3109	22	16	16	100.0	87.5	0(0.0)	14	0(0.0)
3110	Non-pregnant							
3111	22	15	15	100.0	93.3	0(0.0)	14	0(0.0)
3112	21	20	20	100.0	100.0	0(0.0)	20	0(0.0)
Total		179	179			1	165	0
Mean	21.7	16.3	16.3	100.0	92.4	(0.8)	15.0	(0.0)
S.D.	0.5	1.6	1.6	0.0	5.6	(2.5)	2.4	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 12-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual delivery data on dams
Dose (mg/kg): 1000

Dam number	Gestation length in days	No. of corpora lutea	No. of implantation sites	Implantation index % a)	Delivery index % b)	No. of stillborns (%)c)	No. of liveborns	External d) abnormalities(%)e)
4101	22	17	17	100.0	94.1	0(0.0)	16	0(0.0)
4102	22	16	16	100.0	93.8	1(6.7)	14	0(0.0)
4103	22	14	14	100.0	100.0	1(7.1)	13	0(0.0)
4104	21	16	16	100.0	100.0	0(0.0)	16	0(0.0)
4105	22	20	19	95.0	94.7	0(0.0)	18	0(0.0)
4106	22	16	16	100.0	100.0	0(0.0)	16	0(0.0)
4107	22	15	15	100.0	100.0	0(0.0)	15	0(0.0)
4108	22	17	16	94.1	87.5	0(0.0)	14	0(0.0)
4109	22	17	17	100.0	100.0	0(0.0)	17	0(0.0)
4110	21	15	15	100.0	80.0	0(0.0)	12	0(0.0)
4111	22	16	16	100.0	93.8	0(0.0)	15	0(0.0)
4112	22	16	16	100.0	93.8	1(6.7)	14	0(0.0)
Total		195	193			3	180	0
Mean	21.8	16.3	16.1	99.1	94.8	(1.7)	15.0	(0.0)
S.D.	0.4	1.5	1.2	2.1	6.1	(3.1)	1.7	(0.0)

a): (No. of implantation sites / No. of corpora lutea)×100
b): (No. of delivered pups / No. of implantation sites)×100
c): (No. of stillborns / No. of delivered pups)×100
d): No. of delivered pups with external abnormalities
e): (No. of delivered pups with external abnormalities / No. of delivered pups)×100

Appendix 13-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 0

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
1101	15	15	100.0	15	14	93.3
1102	13	13	100.0	13	13	100.0
1103	10	10	100.0	10	10	100.0
1104	14	14	100.0	14	14	100.0
1105	10	10	100.0	10	9	90.0
1106	13	13	100.0	13	13	100.0
1107	0	1	0.0			
1108	11	11	100.0	11	11	100.0
1109	17	17	100.0	17	17	100.0
1110	13	13	100.0	13	13	100.0
1111	14	14	100.0	14	14	100.0
1112	15	15	100.0	15	15	100.0
Total	145	146		145	143	
Mean	12.1	12.2	91.7	13.2	13.0	98.5
S.D.	4.3	4.1	28.9	2.2	2.3	3.5

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 40

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups Day 0	No. of live pups Day 4	Viability index on postnatal day 4 % b)
2101	16	16	100.0	16	16	100.0
2102	14	14	100.0	14	14	100.0
2103	17	17	100.0	17	16	94.1
2104	7	7	100.0	7	7	100.0
2105	12	12	100.0	12	12	100.0
2106	16	16	100.0	16	16	100.0
2107	14	15	93.3	14	14	100.0
2108	16	16	100.0	16	16	100.0
2109	Non-pregnant					
2110	Non-pregnant					
2111	16	16	100.0	16	14	87.5
2112	Not copulated					
Total	128	129		128	125	
Mean	14.2	14.3	99.3	14.2	13.9	98.0
S.D.	3.1	3.1	2.2	3.1	2.9	4.4

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 200

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
3101	18	18	100.0	18	17	94.4
3102	14	14	100.0	14	14	100.0
3103	14	14	100.0	14	12	85.7
3104	15	15	100.0	15	15	100.0
3105	15	15	100.0	15	15	100.0
3106	14	14	100.0	14	14	100.0
3107	11	12	91.7	11	11	100.0
3108	16	16	100.0	16	16	100.0
3109	14	14	100.0	14	14	100.0
3110	Non-pregnant					
3111	14	14	100.0	14	14	100.0
3112	20	20	100.0	20	19	95.0
Total	165	166		165	161	
Mean	15.0	15.1	99.2	15.0	14.6	97.7
S.D.	2.4	2.2	2.5	2.4	2.2	4.5

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 13-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual viability index of pups
Dose (mg/kg): 1000

Dam number	No. of live-borns	No. of delivered pups	Live birth index % a)	No. of live pups		Viability index on postnatal day 4 % b)
				Day 0	Day 4	
4101	16	16	100.0	16	15	93.8
4102	14	15	93.3	14	14	100.0
4103	13	14	92.9	13	13	100.0
4104	16	16	100.0	16	16	100.0
4105	18	18	100.0	18	18	100.0
4106	16	16	100.0	16	16	100.0
4107	15	15	100.0	15	15	100.0
4108	14	14	100.0	14	14	100.0
4109	17	17	100.0	17	17	100.0
4110	12	12	100.0	12	12	100.0
4111	15	15	100.0	15	15	100.0
4112	14	15	93.3	14	14	100.0
Total	180	183		180	179	
Mean	15.0	15.3	98.3	15.0	14.9	99.5
S.D.	1.7	1.5	3.1	1.7	1.7	1.8

a): (No. of liveborns / No. of delivered pups)×100
b): (No. of live pups on postnatal day 4 / No. of liveborns)×100

Appendix 14-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 0

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
1101	9	6	0	0	0.60	0.60	9	5	0.64
1102	4	9	0	0	0.31	0.31	4	9	0.31
1103	6	4	0	0	0.60	0.60	6	4	0.60
1104	8	6	0	0	0.57	0.57	8	6	0.57
1105	5	5	0	0	0.50	0.50	5	4	0.56
1106	6	7	0	0	0.46	0.46	6	7	0.46
1107	0	0	1	0	1.00	-			
1108	5	6	0	0	0.45	0.45	5	6	0.45
1109	6	11	0	0	0.35	0.35	6	11	0.35
1110	7	6	0	0	0.54	0.54	7	6	0.54
1111	5	9	0	0	0.36	0.36	5	9	0.36
1112	7	8	0	0	0.47	0.47	7	8	0.47
Total	68	77	1	0			68	75	
Mean	5.7	6.4	0.1	0.0	0.52	0.47	6.2	6.8	0.48
S.D.	2.3	2.8	0.3	0.0	0.18	0.10	1.5	2.2	0.11

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 14-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 40

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
2101	8	8	0	0	0.50	0.50	8	8	0.50
2102	7	7	0	0	0.50	0.50	7	7	0.50
2103	9	8	0	0	0.53	0.53	8	8	0.50
2104	4	3	0	0	0.57	0.57	4	3	0.57
2105	5	7	0	0	0.42	0.42	5	7	0.42
2106	8	8	0	0	0.50	0.50	8	8	0.50
2107	7	7	1	0	0.53	0.50	7	7	0.50
2108	5	11	0	0	0.31	0.31	5	11	0.31
2109	Non-pregnant								
2110	Non-pregnant								
2111	11	5	0	0	0.69	0.69	9	5	0.64
2112	Not copulated								
Total	64	64	1	0			61	64	
Mean	7.1	7.1	0.1	0.0	0.51	0.50	6.8	7.1	0.49
S.D.	2.2	2.2	0.3	0.0	0.10	0.10	1.7	2.2	0.09

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 14-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 200

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
3101	7	11	0	0	0.39	0.39	7	10	0.41
3102	8	6	0	0	0.57	0.57	8	6	0.57
3103	10	4	0	0	0.71	0.71	8	4	0.67
3104	6	9	0	0	0.40	0.40	6	9	0.40
3105	7	8	0	0	0.47	0.47	7	8	0.47
3106	12	2	0	0	0.86	0.86	12	2	0.86
3107	9	2	0	1	0.75	0.82	9	2	0.82
3108	8	8	0	0	0.50	0.50	8	8	0.50
3109	6	8	0	0	0.43	0.43	6	8	0.43
3110	Non-pregnant								
3111	6	8	0	0	0.43	0.43	6	8	0.43
3112	8	12	0	0	0.40	0.40	7	12	0.37
Total	87	78	0	1			84	77	
Mean	7.9	7.1	0.0	0.1	0.54	0.54	7.6	7.0	0.54
S.D.	1.9	3.3	0.0	0.3	0.16	0.17	1.7	3.2	0.17

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 14-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual sex ratio of pups
Dose (mg/kg): 1000

Dam number	Liveborns		Stillborns		Sex ratio of delivered pups a)	Sex ratio of liveborns b)	Postnatal day 4		Sex ratio of live pups on day 4 c)
	No. of males	No. of females	No. of males	No. of females			No. of males	No. of females	
4101	8	8	0	0	0.50	0.50	8	7	0.53
4102	5	9	1	0	0.40	0.36	5	9	0.36
4103	7	6	0	1	0.50	0.54	7	6	0.54
4104	10	6	0	0	0.63	0.63	10	6	0.63
4105	12	6	0	0	0.67	0.67	12	6	0.67
4106	8	8	0	0	0.50	0.50	8	8	0.50
4107	9	6	0	0	0.60	0.60	9	6	0.60
4108	4	10	0	0	0.29	0.29	4	10	0.29
4109	4	13	0	0	0.24	0.24	4	13	0.24
4110	7	5	0	0	0.58	0.58	7	5	0.58
4111	6	9	0	0	0.40	0.40	6	9	0.40
4112	6	8	1	0	0.47	0.43	6	8	0.43
Total	86	94	2	1			86	93	
Mean	7.2	7.8	0.2	0.1	0.48	0.48	7.2	7.8	0.48
S.D.	2.4	2.2	0.4	0.3	0.13	0.14	2.4	2.3	0.14

a): No. of delivered males / No. of delivered pups
b): No. of liveborn males / No. of liveborns
c): No. of live males on day 4 / No. of live pups on day 4

Appendix 15-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 0

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
1101	6.0	9.4	3.4	5.7	8.2	2.5
1102	6.6	10.8	4.2	6.2	10.4	4.2
1103	6.8	11.1	4.3	6.5	11.0	4.5
1104	6.2	9.2	3.0	5.9	8.5	2.6
1105	7.8	13.3	5.5	7.2	12.5	5.3
1106	7.2	10.9	3.7	6.9	10.9	4.0
1107b)						
1108	7.1	12.8	5.7	6.6	12.0	5.4
1109	6.2	9.9	3.7	5.8	8.8	3.0
1110	5.6	9.5	3.9	5.3	8.6	3.3
1111	6.7	11.4	4.7	6.4	10.4	4.0
1112	6.0	9.3	3.3	5.5	8.6	3.1
Mean	6.6	10.7	4.1	6.2	10.0	3.8
S.D.	0.6	1.4	0.9	0.6	1.5	1.0

Unit: g
a): Postnatal day
b): All pups were stillborn.

Appendix 15-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 40

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
2101	7.0	9.9	2.9	6.3	9.3	3.0
2102	6.2	9.6	3.4	5.5	8.9	3.4
2103	6.0	9.6	3.6	5.9	8.9	3.0
2104	7.3	13.8	6.5	7.1	13.4	6.3
2105	7.1	11.5	4.4	6.8	11.0	4.2
2106	6.3	10.0	3.7	6.0	9.3	3.3
2107	6.7	9.6	2.9	6.4	9.6	3.2
2108	6.2	9.7	3.5	5.7	8.7	3.0
2109	Non-pregnant					
2110	Non-pregnant					
2111	6.6	8.4	1.8	6.4	8.2	1.8
2112	Not copulated					
Mean	6.6	10.2	3.6	6.2	9.7	3.5
S.D.	0.5	1.6	1.3	0.5	1.6	1.2

Unit: g
a): Postnatal day

Appendix 15-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 200

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
3101	6.0	9.2	3.2	5.8	8.7	2.9
3102	7.1	9.6	2.5	6.5	9.0	2.5
3103	6.7	10.9	4.2	6.4	10.4	4.0
3104	7.1	10.8	3.7	6.9	10.8	3.9
3105	6.2	9.1	2.9	5.8	8.3	2.5
3106	6.3	9.0	2.7	5.9	8.0	2.1
3107	6.5	10.9	4.4	6.3	10.8	4.5
3108	6.4	10.8	4.4	6.1	10.4	4.3
3109	6.6	11.1	4.5	6.1	10.4	4.3
3110	Non-pregnant					
3111	6.6	9.2	2.6	6.4	8.8	2.4
3112	5.9	7.5	1.6	5.5	7.1	1.6
Mean	6.5	9.8	3.3	6.2	9.3	3.2
S.D.	0.4	1.2	1.0	0.4	1.3	1.0

Unit: g
a): Postnatal day

Appendix 15-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual body weight of pups
Dose (mg/kg): 1000

Dam number	Male			Female		
	0	4a)	Gain	0	4a)	Gain
4101	6.9	10.1	3.2	6.2	9.8	3.6
4102	6.4	10.4	4.0	6.2	10.1	3.9
4103	7.8	11.4	3.6	7.6	11.3	3.7
4104	6.1	8.8	2.7	5.7	8.3	2.6
4105	6.1	8.4	2.3	5.6	7.7	2.1
4106	6.5	9.7	3.2	6.4	10.1	3.7
4107	7.2	11.0	3.8	6.8	9.9	3.1
4108	7.0	11.2	4.2	6.4	9.6	3.2
4109	7.0	10.4	3.4	6.5	10.1	3.6
4110	6.7	10.5	3.8	6.4	9.9	3.5
4111	6.4	10.3	3.9	6.2	10.1	3.9
4112	7.2	10.6	3.4	6.7	10.5	3.8
Mean	6.8	10.2	3.5	6.4	9.8	3.4
S.D.	0.5	0.9	0.6	0.5	0.9	0.6

Unit: g
a): Postnatal day

Appendix 16-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 0

Dam number	No. of pups examined Total (Male + Female)	Findings
1101	1 (0 + 1)	NAF
1102	0	
1103	0	
1104	0	
1105	1 (0 + 1)	NAF
1106	0	
1107a)		
1108	0	
1109	0	
1110	0	
1111	0	
1112	0	

NAF: No abnormal findings
a): All pups were stillborn.

Appendix 16-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 40

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	0	
2102	0	
2103	0	
2104	0	
2105	0	
2106	0	
2107	0	
2108	0	
2109	Non-pregnant	
2110	Non-pregnant	
2111	1 (1 + 0)	NAF
2112	Not copulated	

NAF: No abnormal findings

Appendix 16-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 200

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	1 (0 + 1)	NAF
3102	0	
3103	2 (2 + 0)	NAF
3104	0	
3105	0	
3106	0	
3107	0	
3108	0	
3109	0	
3110	Non-pregnant	
3111	0	
3112	1 (1 + 0)	NAF

NAF: No abnormal findings

Appendix 16-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in dead pups
Dose (mg/kg): 1000

Dam number	No. of pups examined Total (Male + Female)	Findings
4101	0	
4102	0	
4103	0	
4104	0	
4105	0	
4106	0	
4107	0	
4108	0	
4109	0	
4110	0	
4111	0	
4112	0	

NAF: No abnormal findings

Appendix 17-1 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 0

Dam number	No. of pups examined Total (Male + Female)	Findings
1101	14 (9 + 5)	NAF
1102	13 (4 + 9)	NAF
1103	10 (6 + 4)	NAF
1104	14 (8 + 6)	NAF
1105	9 (5 + 4)	NAF
1106	13 (6 + 7)	NAF
1107a)		
1108	11 (5 + 6)	NAF
1109	17 (6 + 11)	NAF
1110	13 (7 + 6)	NAF
1111	14 (5 + 9)	NAF
1112	15 (7 + 8)	NAF

NAF: No abnormal findings
a): All pups were stillborn.

Appendix 17-2 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 40

Dam number	No. of pups examined Total (Male + Female)	Findings
2101	16 (8 + 8)	NAF
2102	14 (7 + 7)	NAF
2103	16 (8 + 8)	NAF
2104	7 (4 + 3)	NAF
2105	12 (5 + 7)	NAF
2106	16 (8 + 8)	NAF
2107	14 (7 + 7)	NAF
2108	16 (5 + 11)	NAF
2109	Non-pregnant	
2110	Non-pregnant	
2111	14 (9 + 5)	NAF
2112	Not copulated	

NAF: No abnormal findings

Appendix 17-3 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 200

Dam number	No. of pups examined Total (Male + Female)	Findings
3101	17 (7 + 10)	NAF
3102	14 (8 + 6)	NAF
3103	12 (8 + 4)	NAF
3104	15 (6 + 9)	NAF
3105	15 (7 + 8)	NAF
3106	14 (12 + 2)	NAF
3107	11 (9 + 2)	NAF
3108	16 (8 + 8)	NAF
3109	14 (6 + 8)	NAF
3110	Non-pregnant	
3111	14 (6 + 8)	NAF
3112	19 (7 + 12)	NAF

NAF: No abnormal findings

Appendix 17-4 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of C.I. Reactive Black-5 by oral administration in rats
Individual externally for gross abnormalities in pups on postnatal day 4
Dose (mg/kg): 1000

Dam number	No. of pups examined Total (Male + Female)	Findings
4101	15 (8 + 7)	NAF
4102	14 (5 + 9)	NAF
4103	13 (7 + 6)	NAF
4104	16 (10 + 6)	NAF
4105	18 (12 + 6)	NAF
4106	16 (8 + 8)	NAF
4107	15 (9 + 6)	NAF
4108	14 (4 + 10)	NAF
4109	17 (4 + 13)	NAF
4110	12 (7 + 5)	NAF
4111	15 (6 + 9)	NAF
4112	14 (6 + 8)	NAF

NAF: No abnormal findings

R-1114

信頼性保証書（1/4）

試験番号　：　R-1114

試験表題　：　リアクティブ ブラック-5のラットを用いた経口投与による反復投与毒性･生殖発生毒性併合試験

本試験は以下に示す基準を遵守して実施されたことを保証致します。

- 「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：薬食発0331第8号、平成23･03･29製局第6号、環保企発第110331010号）

なお、調査は下記の通り実施致しました。

2014年3月24日
株式会社ボゾリサーチセンター
信頼性保証部門 [redacted]

試験における調査

項　目	担当者	調　査　日	試験責任者及び運営管理者への報告日
試験計画書	[redacted]	2013年　8月　5日	2013年　8月　5日
作業予定表・コンピュータプロトコール		2013年　8月 15日	2013年　8月 16日
調製・保存（被験物質）		2013年　8月 22日	2013年　8月 22日
被験液の濃度確認		2013年　8月 23日	2013年　8月 23日
群分け		2013年　8月 26日	2013年　8月 27日
体重・摂餌量測定・投与・一般状態の観察・膣垢検査		2013年　8月 27日	2013年　8月 28日
詳細な一般状態の観察		2013年　8月 29日	2013年　8月 30日

R-1114

信頼性保証書（2/4）

項　目	担当者	調　査　日	試験責任者及び運営管理者への報告日
交配	[redacted]	2013年　9月 11日	2013年　9月 11日
尿検査（尿量・色調・定性・沈渣）		2013年 10月　2日	2013年 10月　2日
分娩・哺育観察・体重測定		2013年 10月　2日	2013年 10月　2日
試験計画書変更書（1）		2013年 10月　3日	2013年 10月　3日
摂水量測定		2013年 10月　3日	2013年 10月　3日
機能検査・握力測定・自発運動量測定		2013年 10月　4日	2013年 10月　7日
採血・剖検		2013年 10月　7日	2013年 10月　7日
病理組織学検査（切り出し）		2013年 10月 15日	2013年 10月 16日
尿検査（総ビリルビン）		2013年 10月 17日	2013年 10月 17日
被験物質の安定性		2013年 10月 28日	2013年 10月 28日
試験計画書変更書（2）		2013年 12月 13日	2013年 12月 14日
免疫組織化学染色標本の作製		2013年 12月 18日	2013年 12月 18日
生データ（被験液の濃度確認、被験物質の安定性）		2014年　1月 24日	2014年　1月 24日
測定レポート（被験液の濃度確認、被験物質の安定性：案）		2014年　1月 24日	2014年　1月 24日
測定レポート（被験液の濃度確認、被験物質の安定性）		2014年　1月 27日	2014年　1月 27日
図・表・付表		2014年　1月 24日 2014年　1月 25日 2014年　1月 26日 2014年　1月 27日 2014年　1月 28日 2014年　1月 29日	2014年　1月 29日
改善確認		2014年　1月 30日	2014年　1月 31日

R-1114

信頼性保証書（3/4）

項　目	担当者	調　査　日	試験責任者及び運営管理者への報告日
最終報告書草案	[redacted]	2014年　1月 24日	
		2014年　1月 26日	
		2014年　1月 29日	2014年　1月 30日
改善確認		2014年　1月 30日	2014年　1月 31日
生データ（入荷～剖検・病理、飼育関係、被験物質関係）		2014年　1月 24日	
		2014年　1月 26日	
		2014年　1月 27日	
		2014年　1月 28日	
		2014年　1月 29日	
		2014年　3月 15日	
		2014年　3月 16日	
		2014年　3月 17日	
		2014年　3月 18日	
		2014年　3月 19日	2014年　3月 20日
改善確認		2014年　3月 20日	2014年　3月 24日
最終報告書		2014年　3月 24日	2014年　3月 24日

R-1114

信頼性保証書（4/4）

プロセス調査

項　目	試験番号	担当者	調　査　日	試験責任者及び運営管理者への報告日
動物入荷	B-7418	[redacted]	2013年　8月　7日	2013年　8月　7日
検疫・馴化	B-7418		2013年　8月　7日	2013年　8月　7日
	B-7418		2013年　8月 15日	2013年　8月 15日
尿検査	B-6425		2013年　7月 10日	2013年　7月 11日
（浸透圧・電解質）	R-1114		2013年 10月 17日	2013年 10月 17日
血液学検査・	B-7427		2013年　7月 19日	2013年　7月 19日
血液化学検査	B-7433		2013年 10月 22日	2013年 10月 23日
病理組織学検査	B-7437		2013年 10月　7日	2013年 10月　7日
（包埋・薄切・染色）	B-7437		2013年 10月　8日	2013年 10月　8日
	B-7014		2013年 10月 11日	2013年 10月 11日