最 終 報 告 書

試験名：Benzenesulfonic acid,4-hydroxy-,tin(2+)salt 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-945

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Table 17　　出生児の生後 4 日剖検所見

4. 要約

Benzenesulfonic acid,4-hydroxy-,tin(2+)salt の 0（対照群）、12、60、及び 300 mg/kg を、Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間及び交配期間を通して剖検前日（42 日間）まで、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して授乳 4 日まで（41~51 日間）投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 300 mg/kg 投与群については 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。

1）反復投与毒性

詳細な一般状態の観察、機能検査、握力測定、自発運動量の測定、体重、摂餌量、尿検査（摂水量を含む）及び血液化学検査に被験物質投与による影響は認められなかった。

一般状態では、300 mg/kg 投与群の雄で投与 4 週以降に投与後の流涎がみられた。

血液学検査では、投与期間終了時検査において、300 mg/kg 投与群の雌でヘモグロビン量及びヘマトクリット値の低値がみられた。

血液化学検査では、投与期間終了時検査において、300 mg/kg 投与群の雄で ALT の高値がみられた。

病理学検査では、投与期間終了時検査において、300 mg/kg 投与群の雌雄で盲腸の拡張、胃の境界縁の肥厚及び十二指腸の粘膜上皮細胞の肥大が認められた。

血液学検査及び病理学検査で見られた変化は、いずれも休薬により回復した。

2）生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかった。更に、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響は認められず、授乳期間中の授乳状態にも異常 認められなかった。

出生児では、外表観察、出生時及び生後 4 日の体重及び生後 4 日剖検所見及び生存率に被験物質投与による変化は認められなかった。

これらの結果から、Benzenesulfonic acid,4-hydroxy-,tin(2+)salt の反復投与毒性に対する無影響量は雌雄ともに 60 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも 300 mg/kg/day 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、Benzenesulfonic acid,4-hydroxy-,tin(2+)salt 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。

6. 試験材料及び方法

6.1 被験物質

Benzenesulfonic acid,4-hydroxy-,tin(2+)salt は
以下の情報とともに供給された（添付資料 1）。

名称	:	Benzenesulfonic acid,4-hydroxy-,tin(2+)salt
CAS 番号	:	70974-33-3
構造式又は示性式	:	$(C_6H_4(OH)SO_3)_2Sn$
分子量	:	465.05
純度	:	96.0%
不純物（原料からの推定値）	:	Benzenesulfonic acid,2-hydroxy-,tin(2+)salt<2% Benzenesulfonic acid,2,4-hydroxy-,tin(2+)salt<2%
性状	:	白色結晶性の粉末
沸点	:	300°C 以上
メタノール溶状（1→20）	:	2%以上で白濁
安定性	:	関連試験終了後に被験物質製造者にて純度を確認した結果、安定性に問題はなかった（添付資料 2）。
保存方法	:	冷暗所（冷蔵庫内、許容値：1~10°C、実測値：2~8°C）
保存場所	:	御殿場研究所　被験物質保存室及び第 1 研究棟 2 階被験物質調製室
残量の処置	:	被験物質 5g を保存試料として御殿場研究所 被験物質保存室に保存し、動物試験終了後の残量はすべて大和化成株式会社に返却した。

6.2 被験液の調製

6.2.1 被験液の調製及び保存方法

濃度ごとに必要量の被験物質を秤量し、注射用水（株式会社大塚製薬工場、ロット番号：6A80）に徐々に加えて懸濁して 2.4、12 及び 60mg/mL 液を調製した。調製は 7 日間に 1 回以上の頻度で行い、使用時まで遮光容器（褐色ガラス瓶）に入れて冷暗所（冷蔵庫内、実測値：3~6°C）で保存し、使用前に室温に戻した。残液は吸水性のよいもの（新聞紙、ペーパータオル等）に吸収させて焼却処分した。

6.2.2 被験液の安定性

本被験物質の2及び200 mg/mL懸濁液（媒体：注射用水）は、遮光容器で冷暗所（冷蔵庫内）8日間保存後室温24時間は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（添付資料3、試験番号：A-1905）。

6.2.3 被験液の濃度・均一性確認

雄の投与第1週と投与最終週に用いる各濃度液について、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分析した。その結果、各濃度液ともに表示値に対する被験物質の割合は94.5~107.5%、C.V.値は0.0~2.3%であり、いずれも許容範囲内（濃度：表示値に対する割合±10%、C.V.：10%以下）であった（添付資料4、5）。

[測定対象標準物質]

製造者	:	大和化成株式会社
名称	:	Benzenesulfonic acid,4-hydroxy-,tin(2+)salt
ロット番号	:	060501
保存方法	:	冷暗所（冷蔵庫内、許容値：1~10°C、実測値：2~8°C）
保存場所	:	御殿場研究所　被験物質保存室及び生化学部標準物質保存場所

[分析方法]

以下の表に従って希釈し、測定実測試料を調製した。なお、1次希釈ではテトラヒドロフランを、2次希釈及び3次希釈ではテトラヒドロフラン/蒸留水（9:1、v/v）を用いて希釈した。測定試料の採取はマグネチックスターラーで撹拌しながらn=1で行った。

測定試料 (mg/mL)	1次希釈		2次希釈		3次希釈		希釈率
	採取量 (mL)	定容量 (mL)	採取量 (mL)	定容量 (mL)	採取量 (mL)	定容量 (mL)	
2.4	1	10	2	10	–	–	50
12	1	10	1	25	–	–	250
60	1	10	1	30	2.5	10	1200

[使用機器]

分光光度計　　U-1100　（株式会社　日立製作所）

[分光光度法測定条件]

測定波長	:	271 nm
対照試料	:	テトラヒドロフラン/蒸留水（9:1、v/v）

[測定値の算出]

標準試料溶液の吸光度を3回、測定実測試料の吸光度をそれぞれ1回ずつ測定し、以下の式により測定試料中のBenzenesulfonic acid, 4-hydroxy-, tin (2+) salt濃度を求めた。

$$\text{測定試料中 Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt 濃度 (mg/mL)} = \frac{Qt}{Qs} \times A \times F \times \frac{1}{1000}$$

Qt ： 測定実測試料の Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt の吸光度
Qs ： 標準試料溶液の Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt の平均吸光度
A ： 標準試料溶液中の Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt 濃度 (μg/mL)
F ： 希釈率

6.3 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〕雌雄各70匹を8週齢で購入（入荷匹数：雌雄各73匹）し、15日間の検疫・馴化飼育を行った。その間、一般状態の観察、体重測定及び性周期検査（検疫期間終了後の9日間）を基に、雄は一般状態、雌は一般状態及び性周期にそれぞれ異常がなく、体重増加が良好な各58匹を選択し、10週齢で投与に使用した。投与開始時の体重範囲は雄で340~409g、雌は205~257gであった。

なお、群分けは群分け当日（投与開始の前日）の体重により層別化し、各群の平均体重ができるだけ均等となるよう各群に割り付けた。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）で行った。群分けから除外された動物のうち、雌は無処置動物として14匹を継続飼育した。残りの雄（15匹）及び性周期異常を示した雌（1例）はエーテル深麻酔下で安楽死させた。なお、継続飼育した無処置雌動物14匹は死亡などにより交配すべき相手がいない動物が認められなかったため、交配期間終了後エーテル深麻酔下で安楽死させた。

6.4 飼育条件

動物は、温度21~26°C、相対湿度38~63%、換気回数1時間10~15回、照明1日12時間（07:00~19:00）の動物飼育室（飼育室番号：301号室）でブラケット式金属製網ケージ（W 250×D 350×H 200 mm：日本ケージ株式会社）で個別に、交配期間中は雌雄各1匹の計2匹を収容した。なお、妊娠17日から授乳5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）を入れたプラスチック製エコンケージ（W 340×D 400×H 185 mm：日本クレア株式会社）に個別に収容した。飼料はNMF固形（非滅菌：オリエンタル酵母工業株式会社、ロット番号：060315、060523、060714）

をステンレス製給餌器を用いて自由に摂取させた。飲料水は水道水（御殿場市営水道水：給水瓶使用）を自由に摂取させた。

飼料中の混入物質等については、使用したロットについて財団法人日本食品分析センターで実施した分析結果を入手した。また、床敷については、財団法人日本食品分析センターで定期的（年6回）に実施した分析結果を入手した。飲料水については、水道法に準拠した水質の分析を東芝機械環境センター株式会社に定期的（年4回）に依頼し、結果を入手した。これらのデータにより飼料、飲料水及び床敷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。

6.5　動物の識別

動物の個体識別は入荷時に小動物用耳標をつけて行った。群分け後は、飼育ケージに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、動物番号、耳標番号、剖検予定日（主群の雄及び回復群の雌雄）、交尾成立日及び分娩日（主群の雌）を明記した。

6.6　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OECD Guideline for Testing of Chemicals 422に準じ、経口投与を選択した。投与期間は主群の雄及び回復群の雌雄で交配前14日間、交配期間14日間及び交配期間終了後14日間の42日間、主群の雌で交配前14日間、交配期間及び妊娠期間を通して授乳4日までの41~51日間とした。

回復期間は回復群の雌雄で、投与終了後14日間とし、その間休薬した。

6.7　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、フレキシブル胃ゾンデを用いて強制経口投与した(08:22~11:38、ただし、投与時に分娩中であった動物は、分娩終了後の15:24~16:53に投与した）。対照群には媒体（注射用水）を同様に投与した。個体ごとの投与液量は最新の体重を基準に算出した。なお、雌の妊娠7日以降については妊娠7日の体重を基準に算出した。

6.8　投与量及び群構成

投与量は12、60及び300 mg/kgとし、これに対照群を加え4群構成とした。1群当たりの動物数は主群の各群で雌雄各 12 匹、回復群は対照群及び高用量群で雌雄各 5 匹とした。群構成表を表1.に示した。

表 1.群構成表

試験群	投与量 (mg/kg)	被験液濃度 (mg/mL)	性	主群		回復群	
				動物数	動物番号	動物数	動物番号
対照群	0	0	雄	12	1001~1012	5	1013~1017
			雌	12	1101~1112	5	1113~1117
低用量群	12	2.4	雄	12	2001~2012	–	–
			雌	12	2101~2112	–	–
中用量群	60	12	雄	12	3001~3012	–	–
			雌	12	3101~3112	–	–
高用量群	300	60	雄	12	4001~4012	5	4013~4017
			雌	12	4101~4112	5	4113~4117

6.9 投与量の設定根拠

先に実施した「Benzenesulfonic acid,4-hydroxy-,tin(2+)salt のラットを用いた 14 日間反復経口投与毒性試験（予備試験）」（投与量：100、300 及び 1000 mg/kg、株式会社ボゾリサーチセンター、試験番号：C-R052）では、100 mg/kg で胃の境界縁の肥厚が雌雄 2/5 例に、300 mg/kg 以上の投与群では胃の境界縁の肥厚及び盲腸の拡張がほぼ全例にみられ、更に 1000 mg/kg においては、投与初期に雄の体重及び雌雄の摂餌量の低値、AST 及び ALT の増加などがみられた [1)]。したがって、本試験では長期投与での消化管への被験物質投与による影響が予想され、死亡の多発はないと推察される 300 mg/kg を高用量とし、以下公比 5 で除して 60 及び 12 mg/kg の 3 用量を設定した。

6.10 観察及び検査の方法

試験日の起算は下記の通りとした。

投与開始日	：投与第 1 日
交尾成立日	：妊娠 0 日
交尾までに要した日数	：交配開始日を 0 日として起算
分娩終了日	：授乳 0 日
回復開始日（投与期間終了の翌日）	：回復第 1 日

6.10.1 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、投与直後及び投与約 2 時間後）、回復期間中は毎日 1 回（午前中）、それぞれ体外表、栄養状態、姿勢、行動及び排泄物の異常などの一般状態を観察した。

6.10.2 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、投与開始前に 1 回、全個体について行った。また、主群の雄は投与期間中毎週 1 回、雌は交配前投与期間中及び交配期間中は毎週 1 回、妊娠期間中及び授乳期間中は指定された日（妊娠 1、7、14 及び 20 日、授乳 4 日）にそれぞれ行った。回復群は投与期間中及び回復期間中毎週 1 回行った。機能検査、握力及

び自発運動量の測定は主群の雄で投与終了週（投与 36 日）に、主群の雌で授乳 4 日（投与 42、43 日）の F1 児剖検後に、回復群の雌雄で投与終了週（投与 36 日）及び回復終了週（回復 8 日）に 1 群当たり 5 匹について行った。

上記の観察、検査及び測定は、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、動物をランダムに配置した状態で行った。なお、詳細な一般状態の観察及び機能検査は、実数データ項目以外はスコア化した評点法を用いた。

1) 詳細な一般状態の観察

- ホームケージ内観察
  姿勢、痙攣、異常行動
- 手に持っての観察
  ホームケージからの取り出し易さ、ハンドリングに対する反応、被毛・皮膚の状態（被毛の汚れ、粗毛、外傷、皮膚の色など）、眼球（眼球突出、眼瞼の開き具合）、眼・鼻の分泌物、可視粘膜、自律神経機能（流涙、流涎、立毛、瞳孔径、呼吸）
- オープンフィールド内観察
  覚醒状態、歩行、姿勢、振戦、痙攣、立ち上がり回数、排泄物（排糞数、排尿）、常同行動（身繕い、旋回など）、異常行動（自咬、後方突進など）

2) 機能検査

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

3) 握力測定

機能検査に引き続き、CPU ゲージ MODEL-9502A（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。測定は 1 時間とし、10 分間隔及び 0~60 分の集計を行った。

6.10.3 体重測定

主群の雄は投与第 1、4、8、11、15、18、22、25、29、32、36、39、42 及び剖検日に、回復群の雌雄は主群の雄の測定日に加え回復第 1、4、8、11、14 及び剖検日に、主群の雌は投与第 1、4、8、11、15 日（未交尾動物は投与第 18、22 日にも測定）、妊娠 0、4、7、11、14、17 及び 20 日並びに授乳 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分娩の終了が確認された個体の授乳 0 日の体重測定を除き 08:19~10:32 の間に行った。剖検日には相対器官重量算出のため、前日から約 16 時間絶食させた後の体重を測定した。

6.10.4　　摂餌量測定

全個体について、主群の雄は投与第 1、4、8、11、15、32、36、39 及び 42 日に、回復群の雌雄は主群の雄の測定日に加え回復第 1、4、8、11 及び 14 日に、主群の雌は投与第 1、4、8、11 及び 15 日、妊娠 1、4、7、11、14、17 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 08:36~12:10 の間に行った。

6.10.5　　膣スメア検査

主群の雌の全個体について、投与開始日から交尾が認められるまで毎日膣スメアを採取し、鏡検した。交配前投与期間中は膣スメア像を発情前期、発情期、発情後期及び発情休止期に分類し、発情期像発現回数及び発情期から次の発情期までの日数（性周期）を調べた。交配期間中は膣スメア内の精子の有無を調べた。

6.10.6　　交配方法

交配前投与期間終了後、主群の同一投与群の雌雄を 1:1 で終夜同居させ、翌朝、膣栓形成あるいは膣スメア中に精子を確認したものを交尾成立とみなした。交尾までに要した日数は交配開始日を 0 日と起算した。

6.10.7　　分娩及び授乳観察

1)　母動物の観察

交尾確認雌動物は全例自然分娩させ、分娩状態の異常の有無を観察した。分娩終了の確認は妊娠 21 日から妊娠 25 日の午前中まで 1 日 2 回（午前、午後）行い、妊娠期間を 0.5 日単位で算出した。分娩が午後 5 時に終了していた場合、その日を授乳 0 日とした。妊娠 25 日の午前 10 時までに分娩しなかった 12 mg/kg 投与群の 1 例（動物番号：2112）と 300 mg/kg 投与群の 2 例（動物番号：4107、4110）は、エーテル麻酔下で腹大動脈切断により放血致死させた後剖検を行い、妊娠の有無を確認した。その結果、着床が認められないことから、不妊と判断し、妊娠期間中のデータは統計処理から除外した。分娩が終了した母動物は出生児の児なめ、胎盤及び羊膜の処理の有無を観察し、分娩終了日を授乳 0 日とし、授乳 4 日まで出生児を授乳させ、児集め、営巣及び授乳を指標として授乳状態を観察した。

分娩した母動物は授乳 4 日から一夜（約 16~20 時間）絶食させた授乳 5 日に、各群 5 匹は血液学検査及び血液化学検査のための採血後に、その他の動物はエーテル麻酔下で腹大動脈切断により放血致死させ、黄体数及び着床痕数を数えた。

2)　出生児の観察

出生日に生存児数、死産児数を数えた。出生児は外表異常の有無を観察し、性別を判定して体重を測定した後、母動物に授乳させた。出生児は生死の観察を生後 4 日まで毎日 1 回行った。なお、死産児及び死亡児は廃棄した。

生後 4 日に体重を測定した後、全例をエーテル麻酔下で放血致死させて剖検を行い、

頭部・胸部・腹部を含む全身の器官･組織の異常の有無を調べた。なお、出生児の体重は個体別に体重を測定し、各腹単位で雌雄別に平均値を算出した。

6.10.8　尿検査（摂水量測定を含む）

雄の全個体について、投与最終週（投与37~38日）及び回復終了週（回復9~10日）に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。検査項目は以下の通りである。なお、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時間尿を用いて浸透圧及び尿量の測定を行い、尿量は4時間の尿量及び20時間の尿量を合計して算出した。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。

検査項目	測　定　方　法
pH	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
たん白質	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
ケトン体	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
グルコース	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
潜血	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
ビリルビン	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[a)]
ウロビリノーゲン	ｵｰｼｮﾝｽﾃｨｯｸｽ-7EA試験紙［アークレイ株式会社］[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）
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)：AUTION MINI™ AM-4290（アークレイ株式会社）

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）

6.10.9　血液学検査

最終投与翌日及び回復期間終了日に、前日から一夜（約16~20時間）絶食させた各群雌雄各5匹[注1)]について、エーテル麻酔下に開腹し、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、以下の項目について測定した。なお、全例について、May-Grüenwald-Giemsa染色法による血液塗抹標本を作製した。ただし、プロトロンビン時間、活性化部分トロンボプラスチン時間及びフィブリノーゲン量については、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（3,100 rpm、1,690×g、12分間）して得られた血漿を

用いて測定した。

検査項目	測 定 方 法	単 位
赤血球数	2角度レーザーフローサイトメトリー法[c)]	$10^4/\mu L$
ヘモグロビン量	シアンメトヘモグロビン変法[c)]	g/dL
ヘマトクリット値	赤血球数及び平均赤血球容積から算出[c)]	%
平均赤血球容積	2角度レーザーフローサイトメトリー法[c)]	fL
平均赤血球血色素量	赤血球数及びヘモグロビン量から算出[c)]	pg
平均赤血球血色素濃度	ヘモグロビン量及びヘマトクリット値から算出[c)]	g/dL
網赤血球率	RNA染色によるレーザーフローサイトメトリー法[c)]	%
血小板数	2角度レーザーフローサイトメトリー法[c)]	$10^4/\mu L$
白血球数	2角度レーザーフローサイトメトリー法[c)]	$10^2/\mu L$
白血球百分率	ペルオキシダーゼ染色によるレーザー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[c)]	%
各白血球細胞の絶対数[注2)]	ペルオキシダーゼ染色によるレーザー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[c)]	$10^2/\mu L$
プロトロンビン時間	クロット法[d)]	s
活性化部分トロンボプラスチン時間	クロット法[d)]	s
フィブリノーゲン量	トロンボプラスチン法[d)]	mg/dL

使用測定機器

c):総合血液学検査装置 アドヴィア 120 (Siemens Healthcare Diagnostics Inc., Illinois, USA、旧社名 : Bayer Corporation, New York, USA)

d):血液凝固自動測定装置 ACL 100 (Instrumentation Laboratory)

注1) : 主群の検査対象各群雌雄各5匹は以下の例とした。

雄	雌
1001~1005	1101、1102、1103、1105、1112
2001~2005	2102、2106、2107、2110、2111
3001~3005	3104、3106、3109、3110、3112
4001~4005	4101、4104、4105、4111、4112

注2) : 好中球、好酸球、好塩基球、リンパ球、単球及び大型非染色球

6.10.10 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)に取り、遠心分離(3,100 rpm、1,690×g、12分間)して得られた血清を用いて以下の項目について測定した。ただし、AST、ALT、LDH及びγ-GTPについては、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(3,100 rpm、1,690×g、12分間)して得られた血漿を用いて測定した。

検査項目	測 定 方 法	単 位
AlP	Bessey-Lowry 法[e)]	IU/L
総コレステロール	CEH-COD-POD 法[e)]	mg/dL
トリグリセライド	LPL-GK-GPO-POD 法[e)]	mg/dL
リン脂質	PLD-ChOD-POD 法[e)]	mg/dL
総ビリルビン	ビリルビンオキシダーゼ法[e)]	mg/dL
グルコース	グルコースデヒドロゲナーゼ法[e)]	mg/dL
尿素窒素	Urease-LEDH 法[e)]	mg/dL
クレアチニン	Creatininase-creatinase-sarcosine-oxidase-POD 法[e)]	mg/dL
ナトリウム	イオン選択電極法[e)]	mmol/L
カリウム	イオン選択電極法[e)]	mmol/L
塩素	イオン選択電極法[e)]	mmol/L
カルシウム	OCPC 法[e)]	mg/dL
無機リン	モリブデン酸法[e)]	mg/dL
総たん白質	Biuret 法[e)]	g/dL
アルブミン	BCG 法[e)]	g/dL
A/G 比	総たん白質及びアルブミンから算出	
AST(GOT)	UV-rate 法[e)]	IU/L
ALT(GPT)	UV-rate 法[e)]	IU/L
LDH	UV-rate 法[e)]	IU/L
γ-GTP	L-γ-ｸﾞﾙﾀﾐﾙ-3-ｶﾙﾎﾞｷｼ-4-ﾆﾄﾛｱﾆﾘﾄﾞ法[e)]	IU/L

使用測定機器

e)：臨床化学自動分析装置　TBA-120FR 形（株式会社東芝）

6.10.11　病理学検査

1)　剖検及び器官重量測定

全個体について、最終投与翌日及び回復期間終了日に、血液・血液化学検査のために採血した動物（各群雌雄各 5 匹）は採血後に、その他の動物はエーテル麻酔下で腹大動脈切断により放血致死させた後に、それぞれ体外表・頭部・胸部・腹部を含む全身の器官・組織の肉眼による詳細な病理解剖を行い、結果を記録した。なお、雌動物（母動物）は授乳 5 日に黄体数及び着床痕数を数えた。

血液学検査及び血液化学検査の採血を行った各群雌雄各 5 匹について、以下に示す器官（精巣及び精巣上体は全例）の重量（絶対重量）を測定するとともに、絶対重量と剖検時の体重から体重 100g 当たりの相対重量を算出した。なお、*印をつけた両側性の器官については左右別々に測定し、その合計値で評価した。

脳、甲状腺*（上皮小体を含む）、胸腺、心臓、肝臓、脾臓、腎臓*、副腎*、精巣*、精巣上体*

2) 病理組織学検査

全動物について、以下に示す器官・組織をリン酸緩衝 10vol%ホルマリン液で固定、保存した（ただし、精巣及び精巣上体はブアン液で固定した後リン酸緩衝 10vol%ホルマリン液で保存した）。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）染色を行い、このうち対照群及び高用量群の血液・血液化学検査に供した雌雄各 5 匹並びに全動物の肉眼的異常部位について鏡検した（両側性の器官については両側を摘出し、片側を鏡検）。その結果、雌雄の十二指腸に被験物質投与の影響が認められたため、主群及び回復群の全例について鏡検し、正常及び異常所見の代表例を写真撮影した。

大脳、小脳、下垂体、脊髄（胸部）、坐骨神経、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、肺（気管支を含む）、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、肝臓、腎臓、膀胱、精巣、精巣上体、卵巣、子宮、精嚢、胸骨（骨髄を含む）、大腿骨（骨髄を含む）、肉眼的異常部位、個体識別部（耳介）

6.11 統計解析

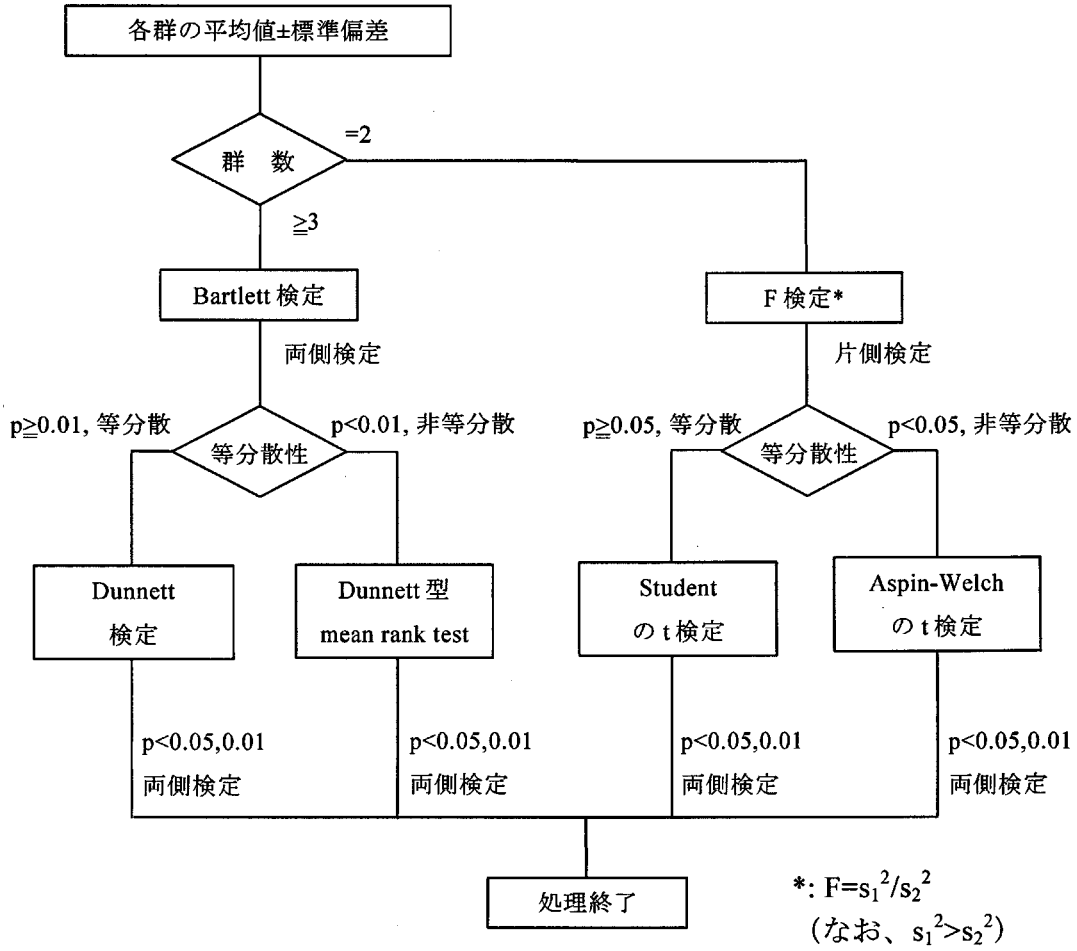
1) 以下の式により各パラメータを算出した。

交尾率(%)=（交尾動物数/同居動物数）×100
受胎率(%)=（妊娠した雌の数/交尾した雌の数）×100
授精率(%)=（妊娠した雌の数/交尾した雄の数）×100
妊娠期間(日)= 授乳 0 日−妊娠 0 日
出産率(%)=（出生児出産雌数/妊娠雌数）×100
着床率(%)=（着床痕数/黄体数）×100
死産児率(%)=（死産児数/総出産児数）×100
出生率(%)=（出生児数/総出産児数）×100
外表異常率(%)=（外表異常児数/出生児数）×100
性比＝雄数/（雄数+雌数）
出生児生存率(%)=（生後 4 日生存児数/生後 0 日出生児数）×100

2) 体重、摂餌量、摂水量、発情期像発現回数、性周期、交尾までに要した日数、妊娠期間、黄体数、着床痕数、出生児数、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、血液学検査、血液化学検査及び器官重量は次に示す模式図の方法に従って検定した。なお、出生児体重（雌雄別）については、母動物ごとの平均値を求めた後、検定を行った[2)3)]。

3) 着床率、死産児率、出生率、外表異常率、出生児生存率は母動物ごとに率を求めた後、Bartlett 検定により等分散性を検定し（有意水準 0.01、両側）、等分散の場合は Dunnett 検定、非等分散の場合は Dunnett 型検定を行った（有意水準 0.05

及び 0.01、両側）[2)3)]。



4) 交尾率、授精率、受胎率、出産率、出生児の性比、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は、各群の交尾動物数、雌を妊娠させた雄動物数、妊娠雌動物数、生存児出産雌動物数、雄生存児数、雌生存児数、正常反射のみられた動物数の合計を求め、イェーツの連続修正による χ^2 検定を行った（有意水準 0.05 及び 0.01、両側）。ただし、期待度数が 5 以下のセルがみられる場合には Fisher の直接確率計算法により検定を行った（有意水準 0.05 及び 0.01、両側）。

7. 試験結果

7.1 一般状態（Table 1-1~1-8、Appendix 1~24）

主群では、300 mg/kg 投与群の雄で投与後の流涎が投与 4 週以降に計 6 例にみられた。

その他の主群及び回復群の動物には異常はみられなかった。

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. 1~6、Table 2-1~2-108、Appendix 25~327）

1) ホームケージ内観察（Table 2-1~2-30、Appendix 25~109）

主群及び回復群のいずれの動物にも異常はみられなかった。

2) 手に持っての観察（Table 2-31~2-60、Appendix 110~194）

主群及び回復群のいずれの動物にも異常はみられなかった。

3) オープンフィールド内観察（Table 2-61~2-90、Appendix 195~279）

主群及び回復群のいずれの動物にも異常はみられなかった。また、立ち上がり回数及び糞数にも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。

4) 機能検査（Table 2-91~2-96、Appendix 280~295）

300 mg/kg 投与群の雌で授乳 4 日に着地開脚幅の有意な低値がみられた。他には主群及び回復群のいずれの動物にも異常はみられなかった。また、空中正向反射に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。

5) 握力測定（Table 2-97~2-102、Appendix 296~311）

主群及び回復群のいずれの動物にも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。

6) 自発運動量の測定（Fig. 1~6、Table 2-103~2-108、Appendix 312~327）

主群では、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。

回復群では、300 mg/kg 投与群の雄で投与 6 週の測定開始 0~30 分の自発運動量に有意な低値がみられたが、同時期の主群の検査に変化はみられなかったことから偶発的変化と判断した。

7.3 体重（Fig. 7~10、Table 3-1~3-8、Appendix 328~351）

主群及び回復群の雌雄ともに体重及び体重増加量には対照群と各投与群との間に有意差は認められなかった。

7.4 摂餌量（Fig. 11~14、Table 4-1~4-8、Appendix 352~375）

主群及び回復群の雌雄ともに摂餌量には被験物質投与による影響は認められなかった。

なお、回復群では、300 mg/kg 投与群の雌雄で一時的に有意な変化が認められたが、体重推移への影響がみられないことから生理的変動範囲内の変化と判断した。

7.5　尿検査（摂水量測定を含む）（Table 5-1~5-8、Appendix 376~393）

定量項目については、主群の 60 mg/kg 投与群で浸透圧に有意な高値がみられたが、投与量に関連した変化ではなかった。その他の検査項目では、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。

定性項目については、主群及び回復群のいずれの動物にも異常はみられなかった。

7.6　血液学検査（Table 6-1~6-8、Appendix 394~401）

1)　投与期間終了時検査

300 mg/kg 投与群の雌でヘモグロビン量及びヘマトクリット値の有意な低値がみられた。なお、同群の雄では平均赤血球血色素量の有意な低値がみられたが、軽度な変化であり、他の赤血球系項目に変化がみられないことから生理的変動範囲内の変化と考えられた。また、60 mg/kg 投与群の雄ではヘモグロビン量の有意な高値が認められたが、発現状況に用量との関連がないことから、生理的変動範囲内の変化と判断した。

2)　回復期間終了時検査

300 mg/kg 投与群の雌でヘモグロビン量及びヘマトクリット値の有意な高値、網赤血球率の有意な低値がみられた。なお、雄動物では対照群と 300 mg/kg 投与群との間に有意差は認められなかった。

7.7　血液化学検査（Table 7-1~7-8、Appendix 402~409）

1)　投与期間終了時検査

300 mg/kg 投与群の雄で ALT の有意な高値、雌で総たん白質の有意な低値が認められた。その他、12 mg/kg 投与群の雄でトリグリセライドの有意な高値が認められたが、発現状況に用量との関連がないことから、生理的変動範囲内の変化と判断した。

2)　回復期間終了時検査

300 mg/kg 投与群の雄で AlP の有意な高値、雌でクレアチニンの有意な低値及び総たん白質の有意な高値が認められたが、投与期間終了時にみられない変化であることから、生理的変動範囲内の変化と判断した。

7.8　器官重量（Table 8-1~8-8、Appendix 410~439）

投与期間終了時検査では絶対及び相対重量の双方において、用量に関連した同一方向の変化（増加又は減少）はみられなかった。なお、以下の器官に対照群との間に有意差がみられたが、いずれも相対重量のみの軽度な変化であり生理的変動範囲内の変化と考えられた。

1)　投与期間終了時検査

胸腺　：　相対重量の有意な高値が 60 mg/kg 投与群の雄にみられた。

2)　回復期間終了時検査

肝臓　：　相対重量の有意な高値が 300 mg/kg 投与群の雌雄にみ

られた。

腎臓　：　相対重量の有意な高値が 300 mg/kg 投与群の雌雄にみられた。

7.9　剖検所見（Table 9-1、9-2、Appendix 440~555）

1)　投与期間終了時検査

被験物質投与によると考えられる変化が雌雄の盲腸及び胃にみられた。

盲腸　：　拡張が 300 mg/kg 投与群の雄 8 例と雌 2 例にみられた。

胃　：　境界縁の肥厚が 300 mg/kg 投与群の雄 4 例と雌 2 例にみられた。

他に、以下の器官・組織に所見がみられたが、出現頻度及び病理学的性状から偶発的変化と考えられた。

回腸　：　憩室が 12 mg/kg 投与群の雄 1 例にみられた。

腎臓　：　白色巣が 12 mg/kg 投与群の雄 1 例にみられた。

下垂体　：　嚢胞が 300 mg/kg 投与群の雌 1 例にみられた。

胃　：　漿膜の結節が 60 mg/kg 投与群の雄 1 例と 300 mg/kg 投与群の雌 1 例に、腺胃の暗赤色巣が対照群の雌 1 例にみられた。

尿道　：　結節が 12 mg/kg 投与群の雌 1 例にみられた。

2)　回復期間終了時検査

回腸　：　憩室が対照群の雄 1 例にみられた。

腎臓　：　嚢胞が対照群の雄 1 例にみられた。

脾臓　：　隆起巣が 300 mg/kg 投与群の雄 1 例にみられた。

7.10　病理組織学検査（Table 10-1~10-4、Appendix 440~555）

1)　投与期間終了時検査

被験物質投与によると考えられる変化が十二指腸にみられた。肉眼的変化がみられた盲腸及び胃には被験物質投与の影響はみられなかった。

十二指腸　：　軽微な粘膜上皮細胞の肥大が 300 mg/kg 投与群の雄 6 例と雌 5 例にみられた。

その他、以下の所見がみられたが、出現状態及び病理組織学的性状から偶発病変と考えられた。

精巣上体　：　軽微な間質細胞浸潤が対照群の雄 1 例にみられた。

心臓　：　軽微な心筋炎症巣が対照群と 300 mg/kg 投与群の雄各 1 例にみられた。

回腸　：　軽度な憩室が 12 mg/kg 投与群の雄 1 例にみられた。

盲腸　：　軽微又は軽度な粘膜の細胞浸潤が対照群の雌雄各 1 例と 300 mg/kg 投与群の雄 3 例にみられた。

腎臓 : 軽微な再生尿細管が対照群の雄3例と300 mg/kg投与群の雄1例に、軽微な限局性線維化が300 mg/kg投与群の雌1例にみられた。

肝臓 : 軽微な微小肉芽腫が対照群の雄 4 例と雌 1 例、300 mg/kg投与群の雄3例と雌2例にみられた。

肺（気管支を含む） : 軽微な泡沫細胞の集簇が対照群及び300 mg/kg投与群の雌各1例にみられた。

下垂体 : 軽度な前葉の嚢胞が300 mg/kg投与群の雌1例にみられた。

脾臓 : 軽微な髄外造血が対照群の雄 3 例と雌 5 例及び300 mg/kg投与群の雄1例と雌5例にみられた。

胃 : 軽微又は軽度な上皮の嚢胞が60 mg/kg投与群の雄1例と300 mg/kg投与群の雌1例に、軽微な腺胃の糜爛が対照群の雌1例にみられた。

精巣 : 軽微な精細管の萎縮が300 mg/kg投与群の1例にみられた。

甲状腺 : 軽微な鰓後体の嚢胞が対照群の雌雄各1例にみられた。

膀胱 : 軽微な皮下の細胞浸潤が対照群の雌1例にみられた。

尿道 : 軽度な結石が12 mg/kg投与群の雌1例にみられた。

2) 回復期間終了時検査

回腸 : 軽度な憩室が対照群の雄1例にみられた。

腎臓 : 軽度な尿細管の嚢胞状拡張が対照群の雄1例にみられた。

脾臓 : 軽度な肉芽腫が300 mg/kg投与群の雄1例にみられた。

7.11 性周期（Table 11、Appendix 556~559）

性周期異常の動物はみられず、平均性周期日数に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。

7.12 交配成績（Table 12、Appendix 560~563）

交配開始後4日までに12 mg/kg投与群の1組以外の組み合わせで、残る1組も10日目に交尾が成立し、全組み合わせで交尾が認められた。なお、不妊であった組み合わせは12 mg/kg投与群の1組と300 mg/kg投与群の2組のみであった。したがって、交尾までに要した日数、交尾率、授精率及び受胎率には対照群と各投与群との間に有意差は認められなかった。

7.13　分娩成績及び分娩･授乳状態（Table 13、Appendix 564~567）

分娩状態では、妊娠 21.5~22.5 日に全例が正常に分娩し、出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数及び出生率には有意差は認められなかった。

哺育状態では、いずれの母動物にも巣作り、児集め及び授乳行動に異常はみられなかった。

7.14　出生児の観察（Table 14、Appendix 568~571）

性比、出生時体重及び外表異常率に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、外表観察において、痕跡尾が 300 mg/kg 投与群に 1 例みられたが、出現頻度及び外表異常の種類から自然発生によるものと考えられた。

7.15　出生児の生存率（Table 15、Appendix 572~575）

授乳期間中の死亡児は対照群で 1 例、12、60 及び 300 mg/kg 投与群で 4、2 及び 2 例みられたのみであり、生後 4 日生存率には対照群と各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 576~579）

出生時及び生後 4 日の雌雄体重には対照群と各投与群との間に有意差は認められなかった。

7.17　出生児の生後 4 日剖検所見（Table 17、Appendix 580~583）

いずれの出生児にも異常はみられなかった。

8. 考察

Benzenesulfonic acid,4-hydroxy-,tin(2+)salt の 0（対照群）、12、60、及び 300 mg/kg を、Sprague-Dawley 系 SPF ラットの雄には交配前 14 日間及び交配期間を通して剖検前日（42 日間）まで、雌には交配前 14 日間及び交配期間並びに妊娠期間を通して授乳 4 日まで（41~51 日間）投与し、反復投与毒性及び生殖発生毒性を検討した。更に、0 及び 300 mg/kg 投与群については 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。

1) 反復投与毒性

詳細な一般状態の観察、機能検査、握力測定、自発運動量の測定、体重、摂餌量及び尿検査（摂水量を含む）に被験物質投与による影響は認められなかった。なお、300 mg/kg 投与群の雌で授乳 4 日に着地開脚幅の有意な低値がみられたが、軽度な変化で他の機能検査項目に変化がみられないことから偶発的変化と判断した。

一般状態では、300 mg/kg 投与群の雄で投与 4 週以降に投与後の流涎がみられた。しかし、詳細な一般状態の観察を初めとした各種機能検査で異常はみられなかったことから、中枢性の変化ではなく、一過性の変化（添付資料 6 参照）であることから被験物質の刺激に基づく変化と推察された。

血液学検査では 300 mg/kg 投与群の雌でヘモグロビン量及びヘマトクリット値の低値がみられ、被験物質による貧血が示唆された。ヘモグロビン量及びヘマトクリット値は回復終了時には高値に転じ、網赤血球率の低値もみられたが、これら変化は貧血の回復に伴う変動と考えられた。

血液化学検査では、投与期間終了時検査において、300 mg/kg 投与群の雄で ALT の高値がみられたが、その原因は不明であった。その他、同群の雌では総たん白質の低値がみられたが、アルブミン量及び A/G 比に変化がないことから生理学的な変動範囲内の変化と考えられた。

病理学検査では、投与期間終了時検査において、300 mg/kg 投与群の雌雄で盲腸の拡張及び胃の境界縁の肥厚がみられた。盲腸での変化は腸内細菌叢の変動を、胃での変化は被験物質の刺激性を疑わせる変化であった。十二指腸で粘膜上皮細胞の肥大が 300 mg/kg 投与群の雌雄で認められた。この変化は、粘膜への極めて軽度な障害作用に対する反応性変化である可能性が考えられた。

血液学検査及び病理学検査で見られた変化は、いずれも休薬により回復性がみられたことからいずれも可逆性の変化と考えられた。なお、回復終了時検査で肝臓及び腎臓重量の高値が 300 mg/kg 投与群の雌雄にみられたが、前述のように他の変化に休薬による回復がみられていること、投与終了時には変化はなく、相対重量のみの軽度な変化であることから偶発的な変化と考えられた。

2)　生殖発生毒性

性周期、交尾までに要した日数、交尾率、授精率及び受胎率には被験物質投与の影響は認められなかった。更に出産率、妊娠期間、黄体数、着床痕数、着床率、死産児率、出生児数、出生率及び性比に被験物質投与の影響は認められず、授乳期間中の授乳状態にも異常が認められないことから、300 mg/kg 投与群においても雌雄動物の交尾能、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考えられた。

出生児では、外表観察、出生時及び生後 4 日の体重及び生後 4 日剖検所見及び生存率には被験物質投与による変化は認められなかった。

これらの結果から、Benzenesulfonic acid,4-hydroxy-,tin(2+)salt の反復投与毒性に対する無影響量は雌雄ともに 60 mg/kg/day、生殖発生毒性に対しては雌雄親動物及び児動物に対する無影響量はいずれも 300 mg/kg/day と判断した。

9. 文献

1) Benzenesulfonic acid,4-hydroxy-,tin(2+)salt のラットを用いた 14 日間反復経口投与毒性試験（予備試験）（株式会社ボゾリサーチセンター、試験番号：C-R052、2006 年）

2) Shayne C. Gad and Carrol S. Weil (1994) : Chapter 7. Statistics for Toxicologists, In Principles and Methods of Toxicology (A. Wallace Hayes, ed.), 3rd ed., pp.221-274, Raven Press, Ltd., New York.

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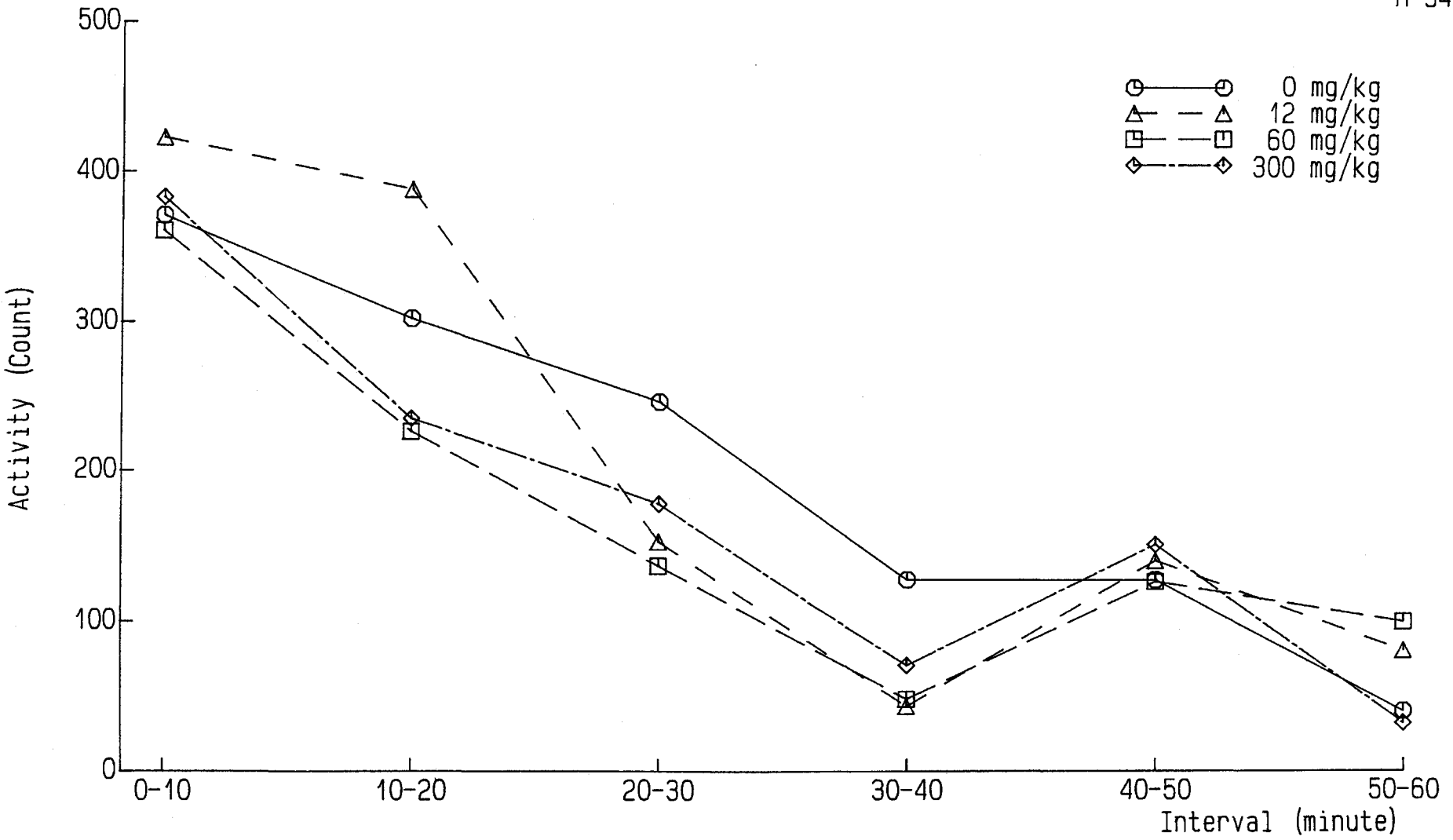

Fig.1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Motor activity of male rats (Main group, Week 6 of administration)

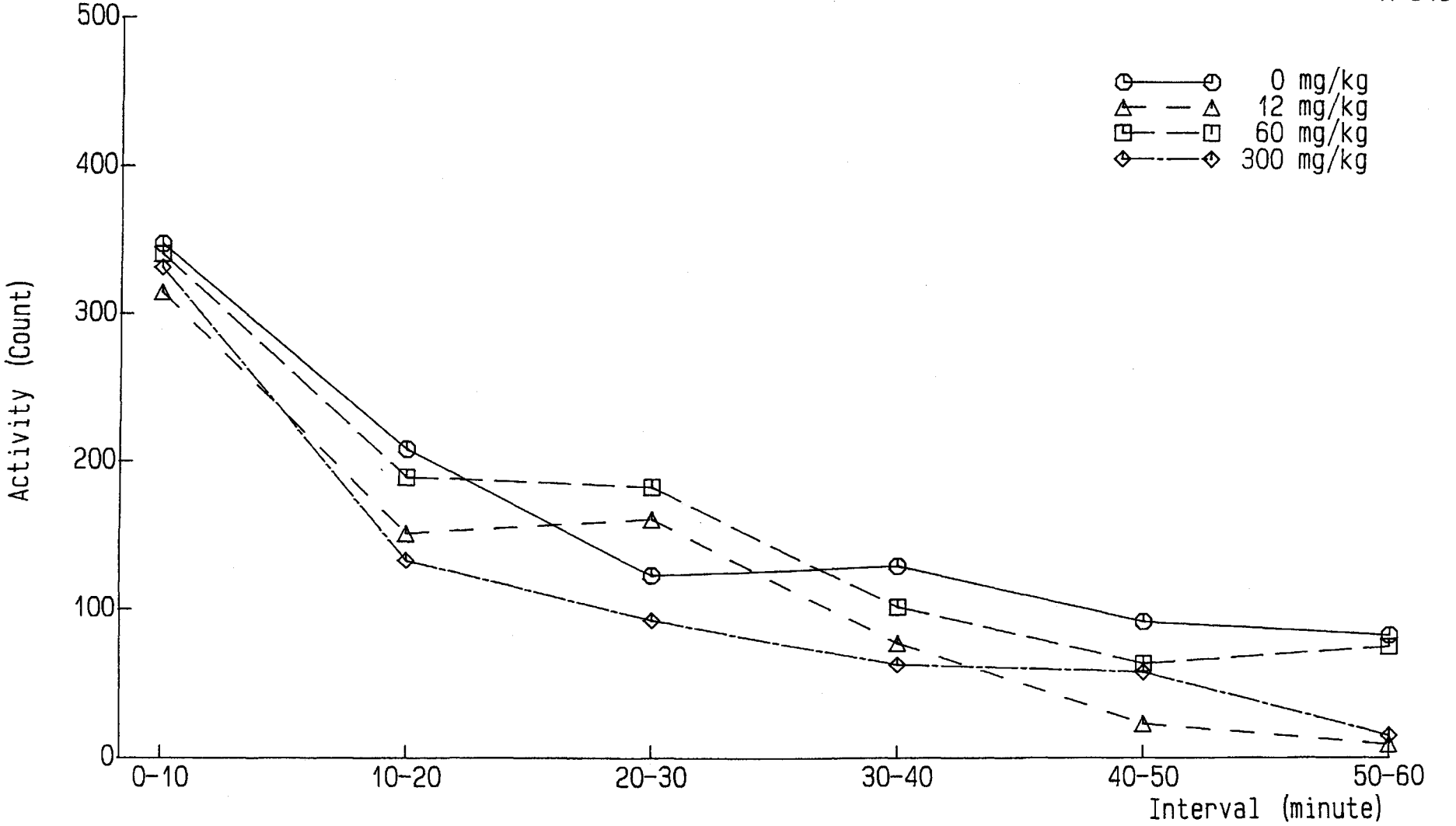

Fig.2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Motor activity of female rats (Main group, Day 4 of lactation)

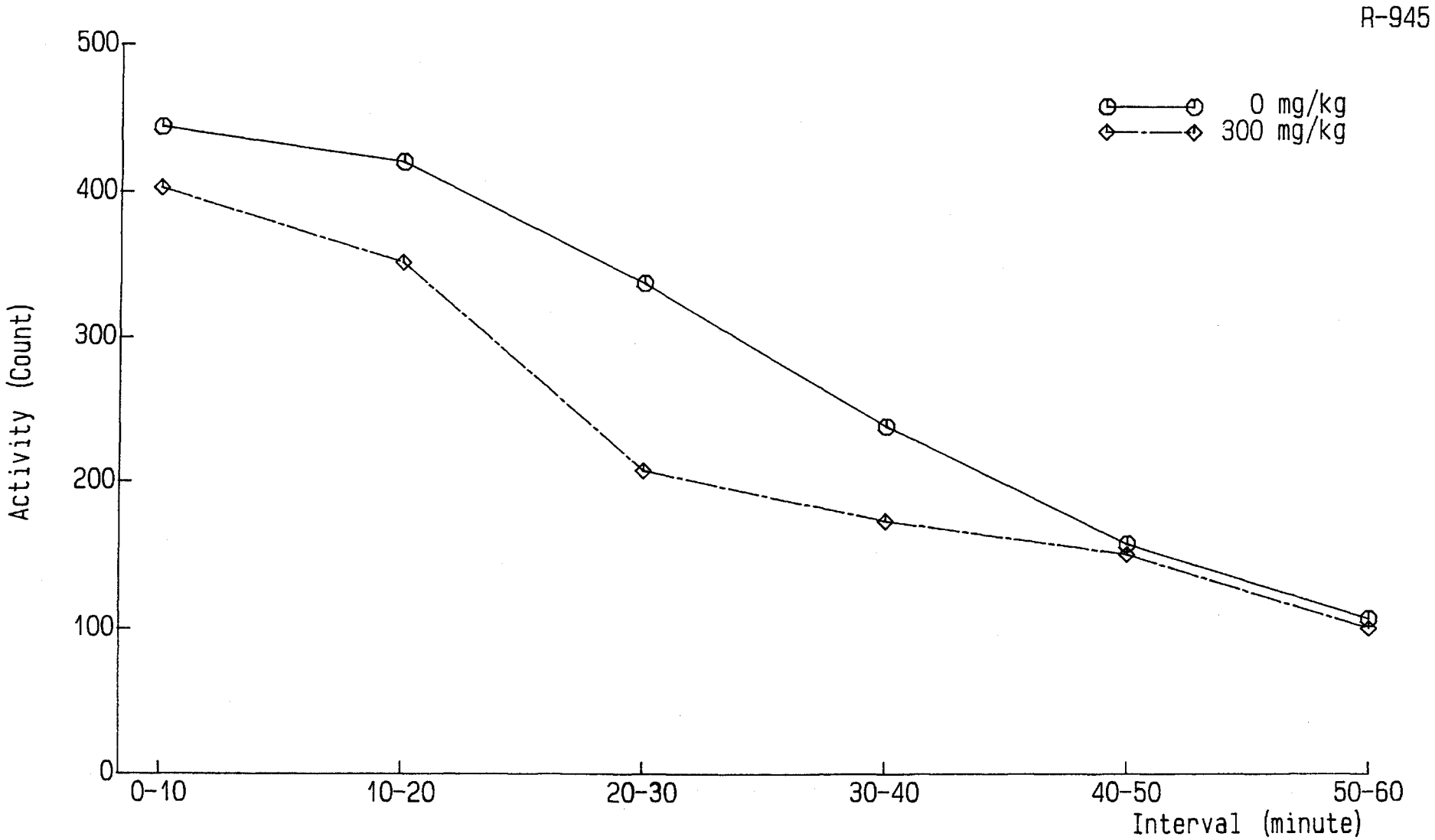

Fig.3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Motor activity of male rats (Recovery group, Week 6 of administration)

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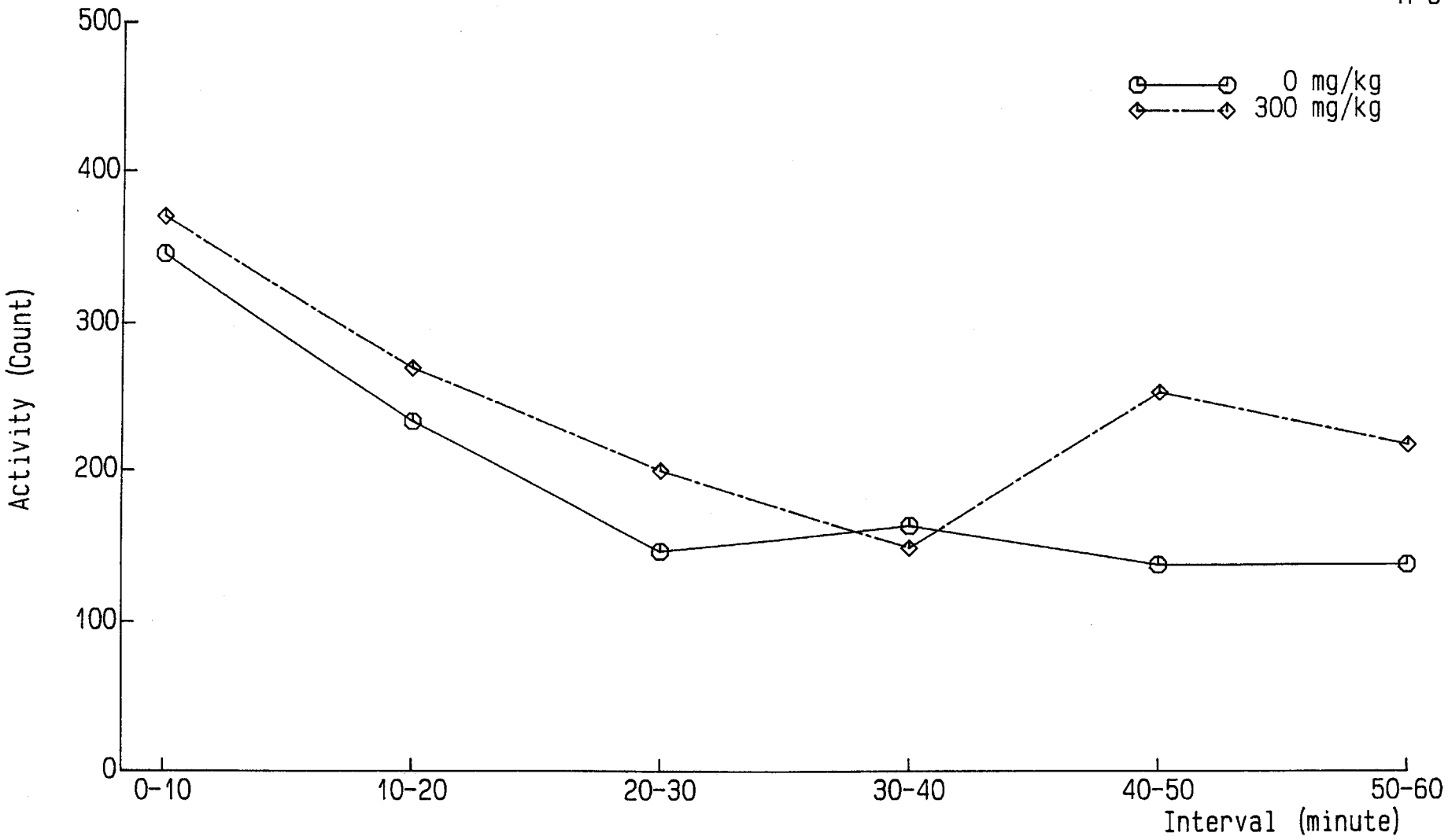

Fig.4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

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

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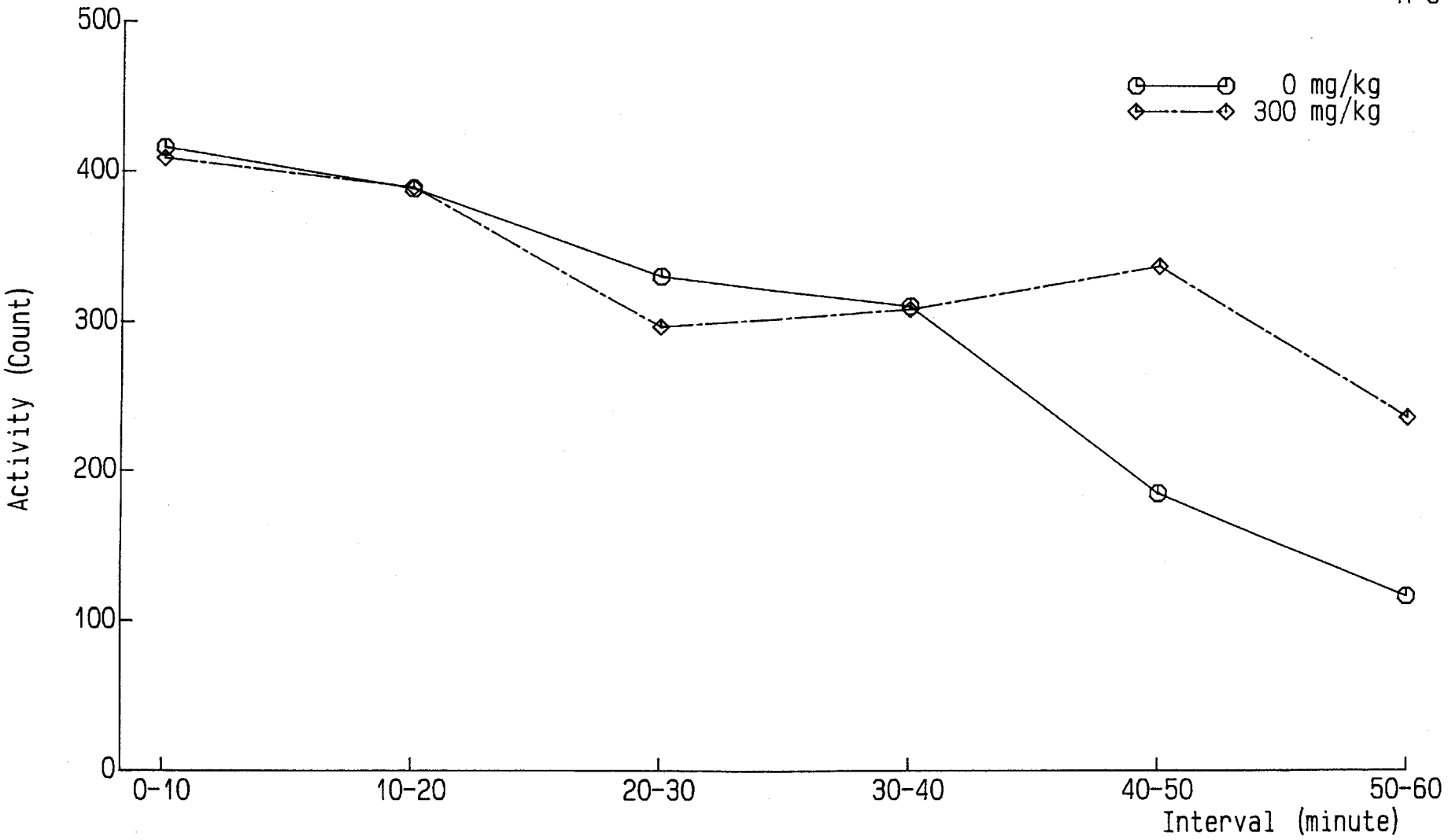

Fig.5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Motor activity of male rats (Recovery group, Week 2 of recovery)

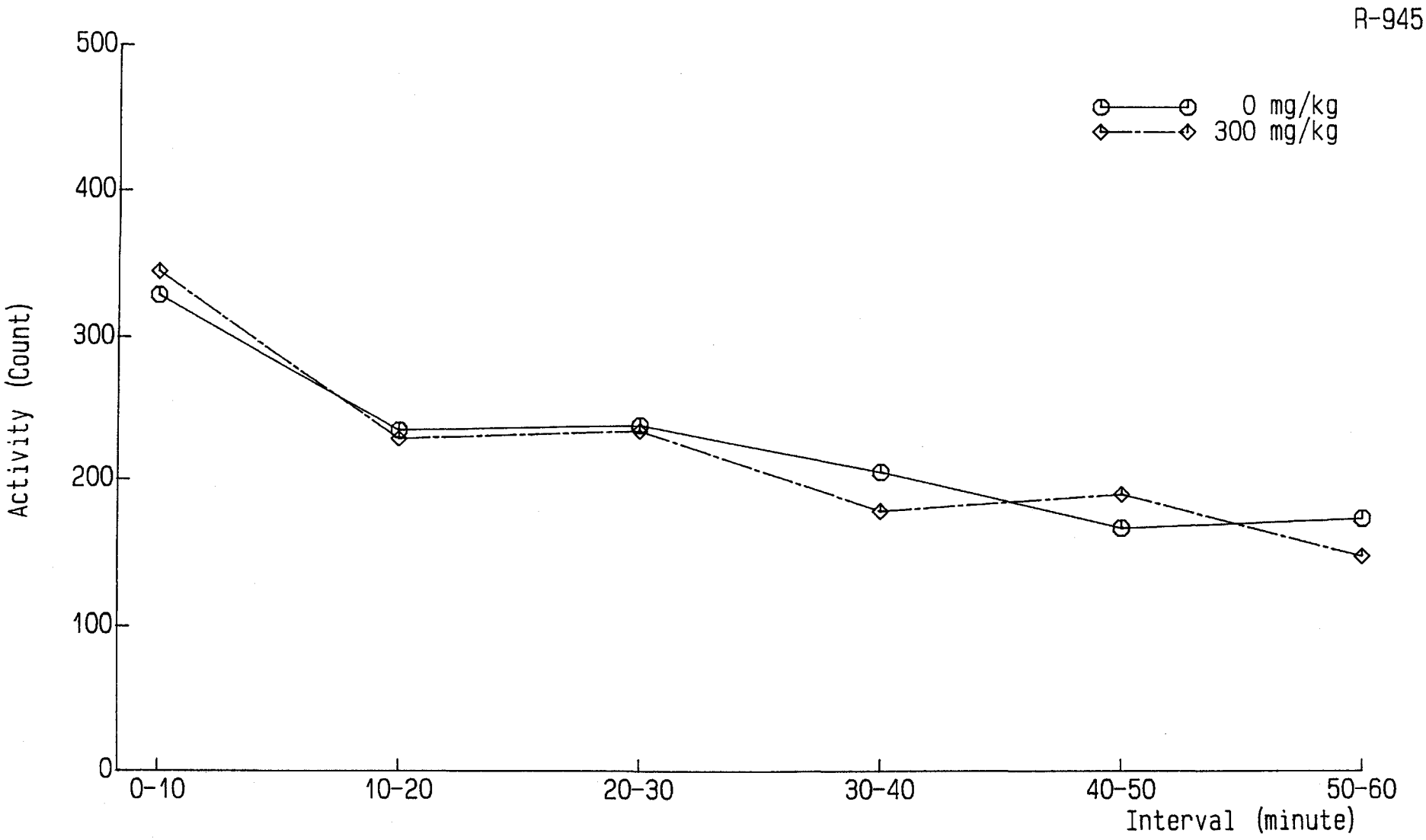

Fig.6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Motor activity of female rats (Recovery group, Week 2 of recovery)

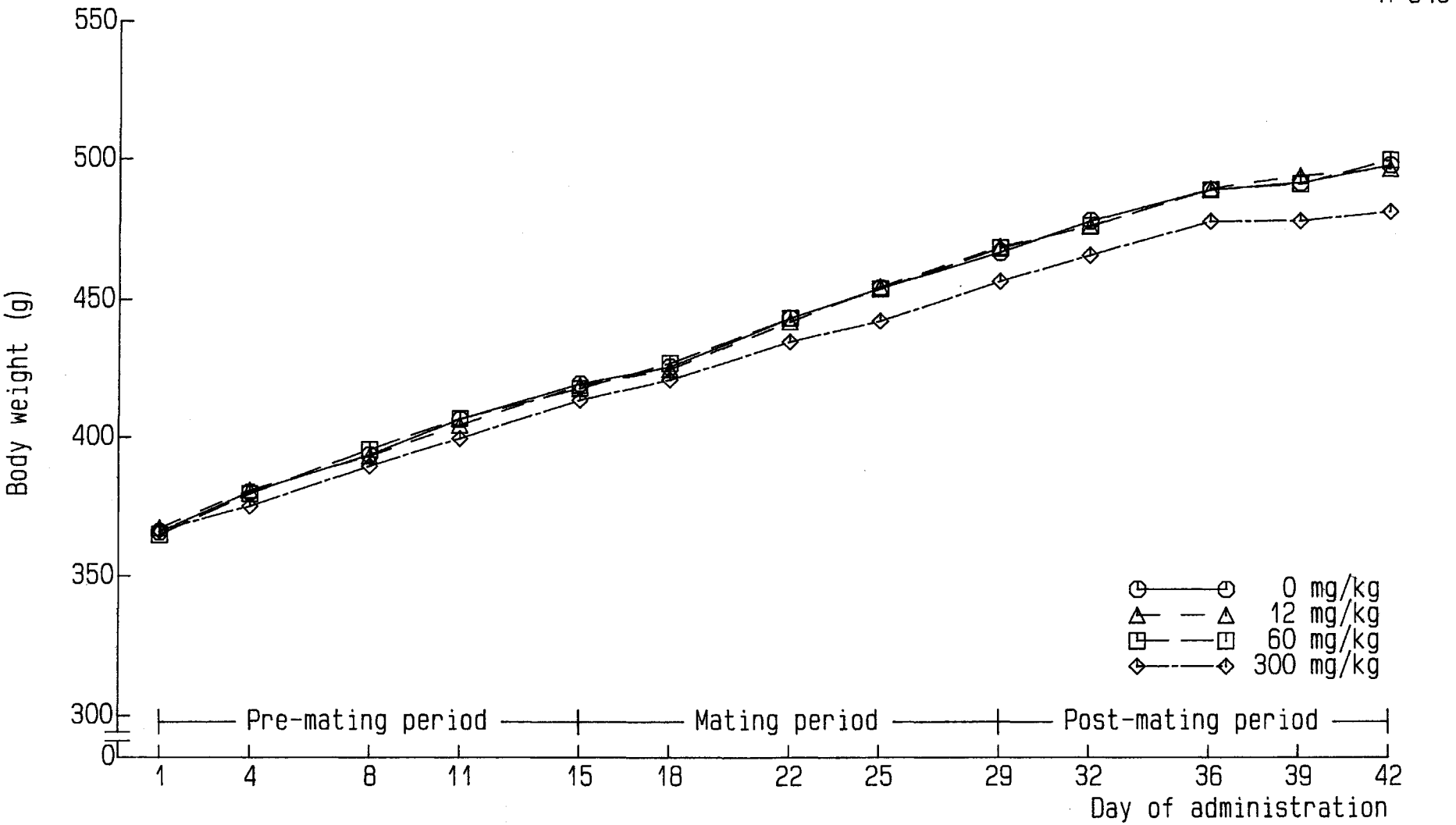

Fig.7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Body weight changes of male rats (Main group)

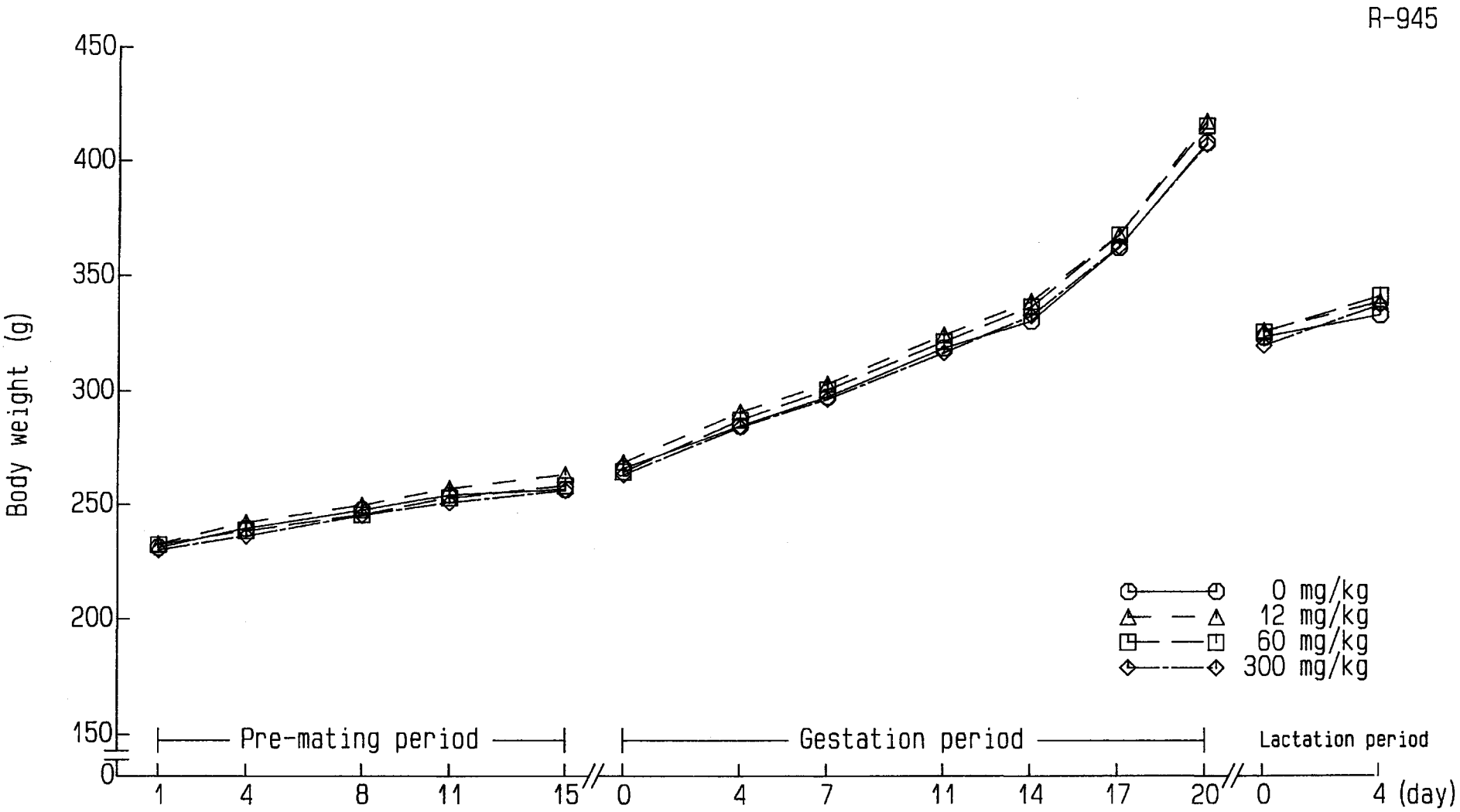

Fig.8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Body weight changes of female rats (Main group)

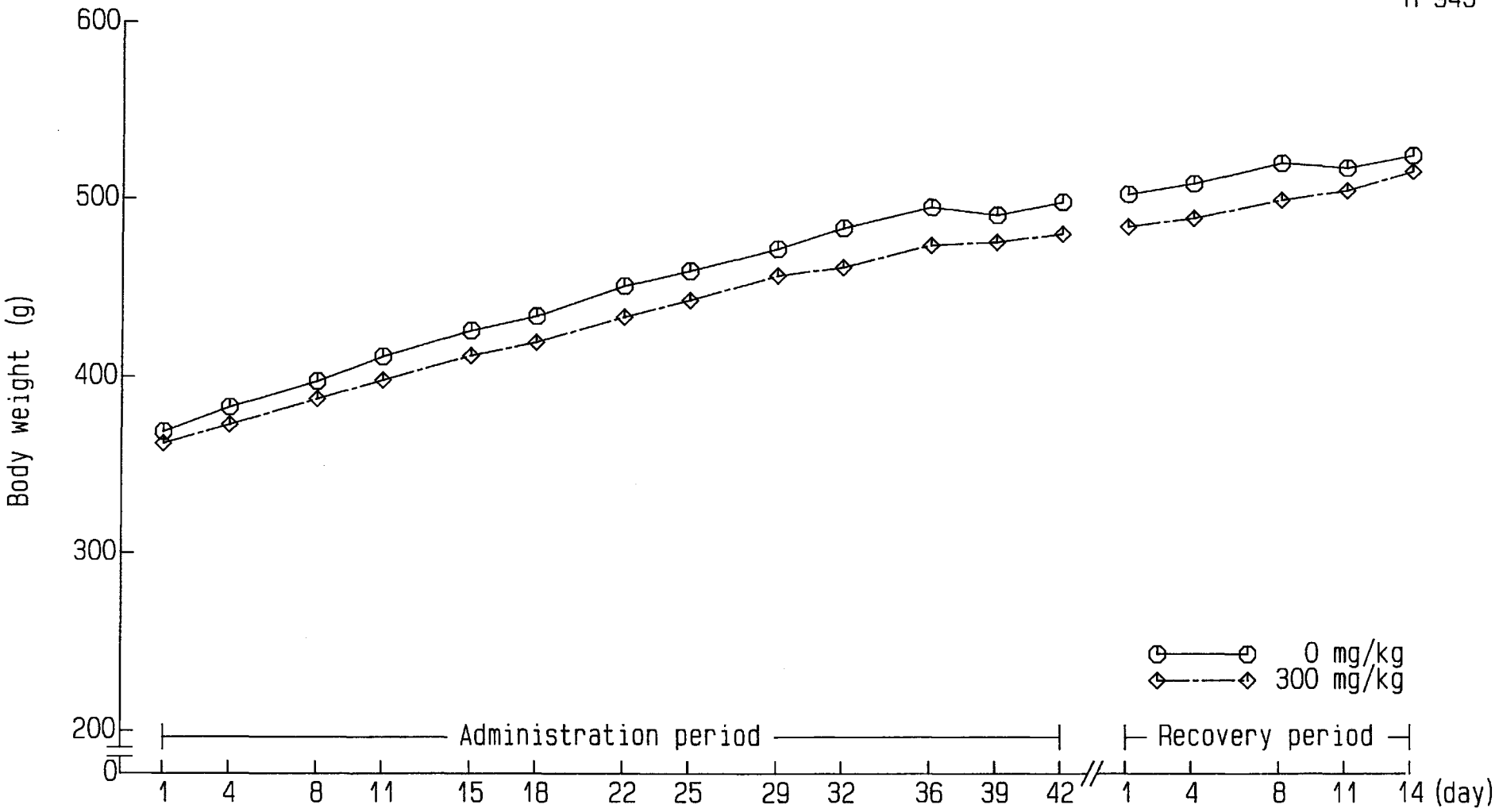

Fig.9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Body weight changes of male rats (Recovery group)

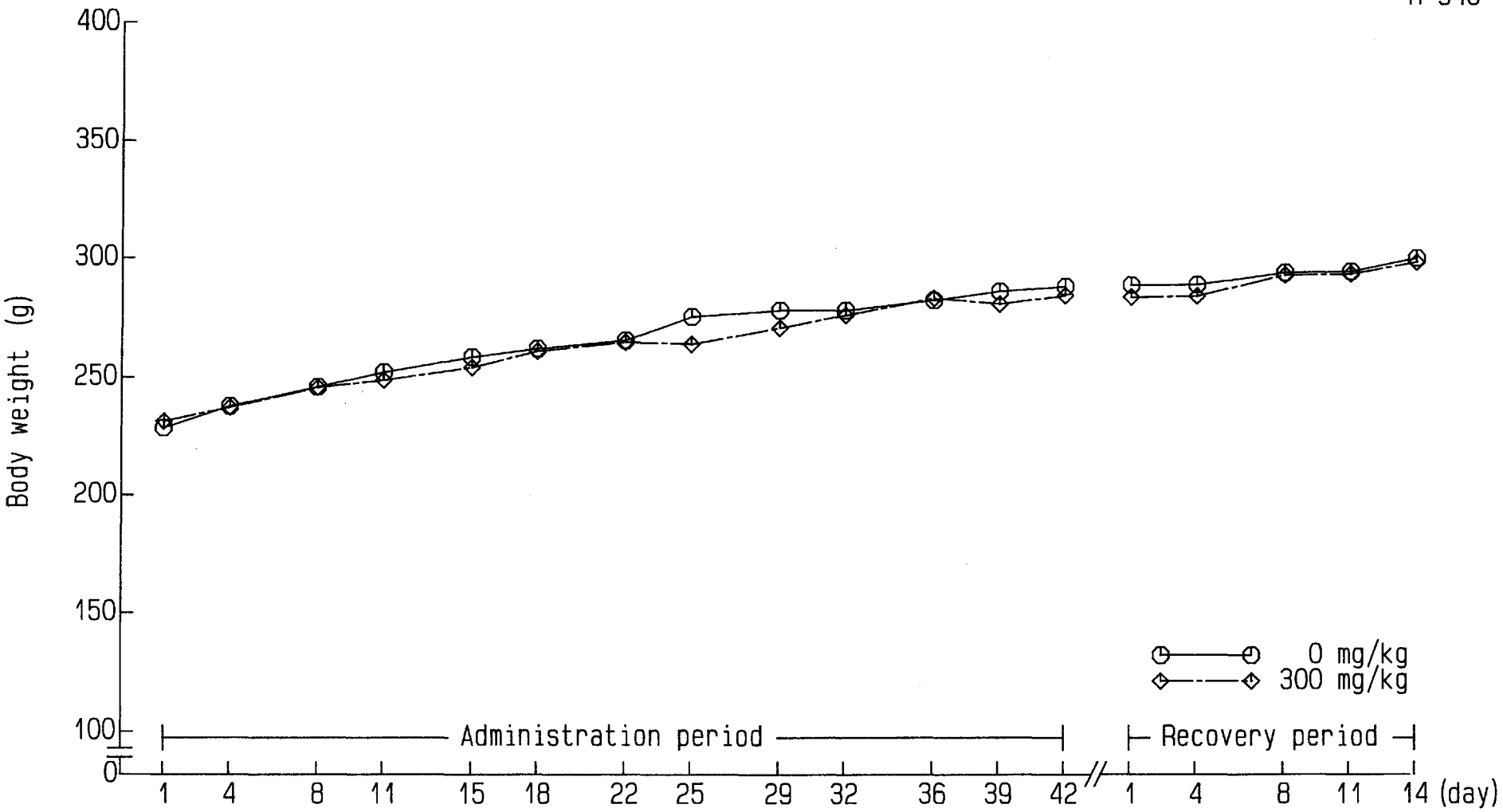

Fig.10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Body weight changes of female rats (Recovery group)

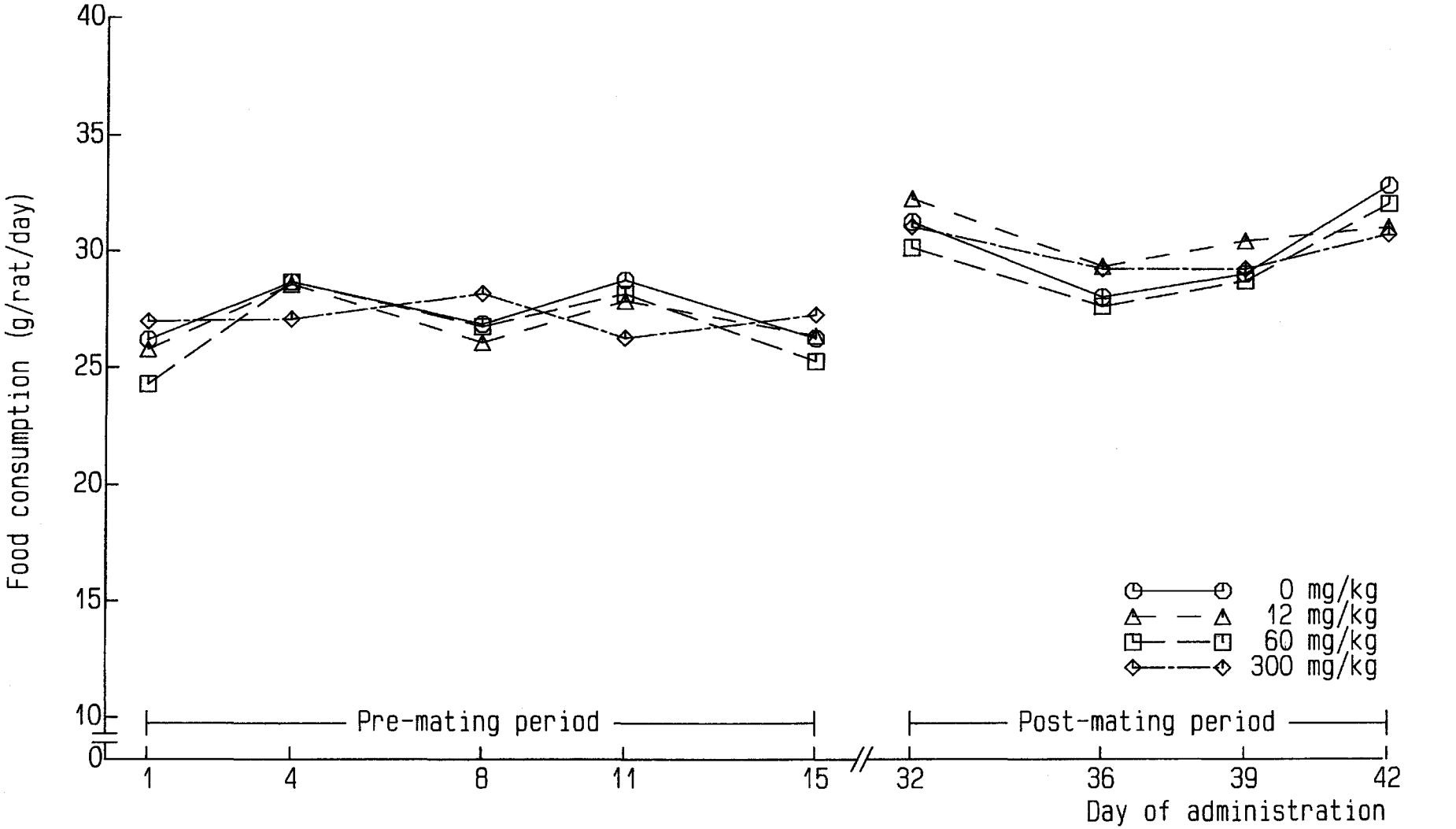

Fig.11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Food consumption of male rats (Main group)

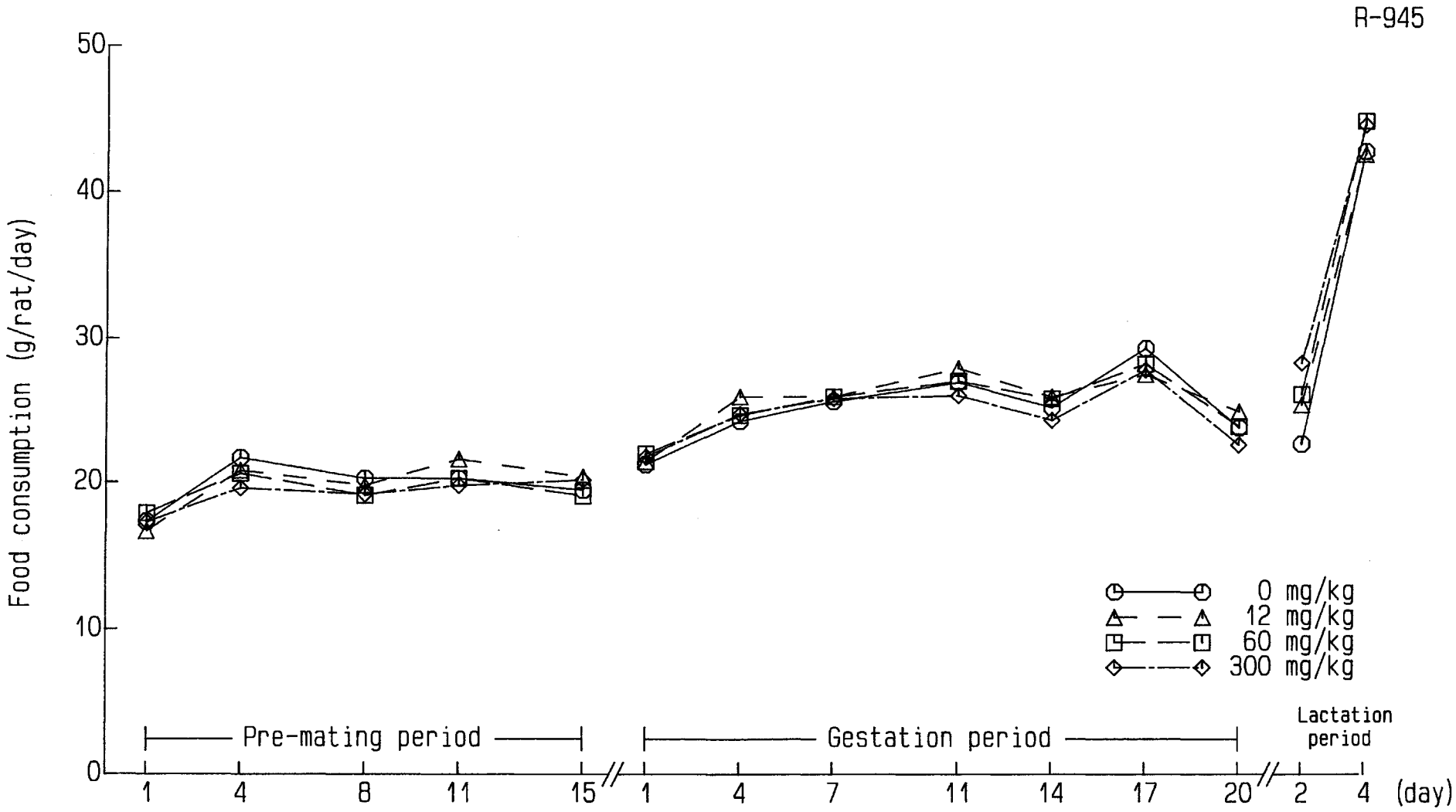

Fig. 12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Food consumption of female rats (Main group)

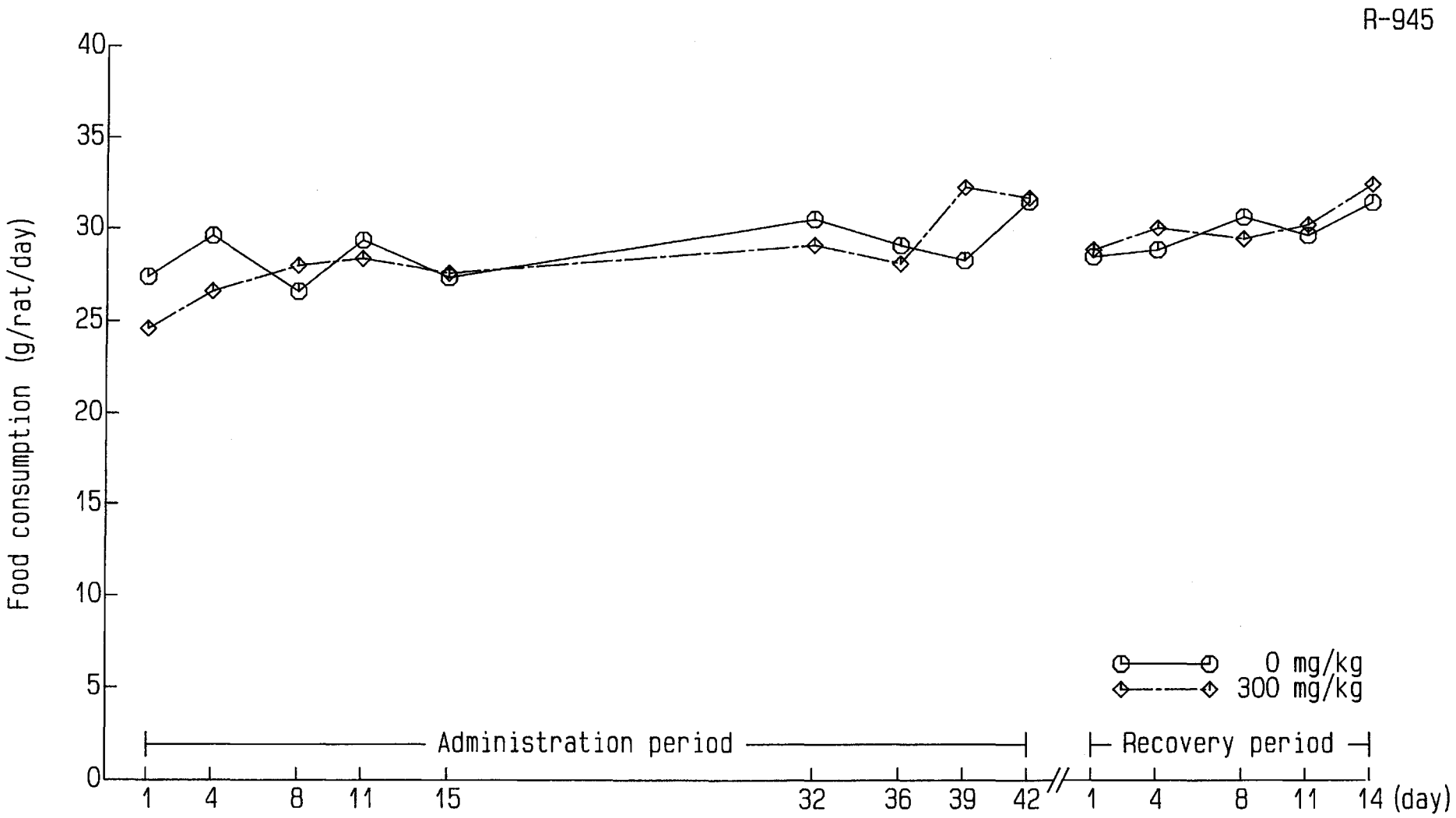

Fig.13 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Food consumption of male rats (Recovery group)

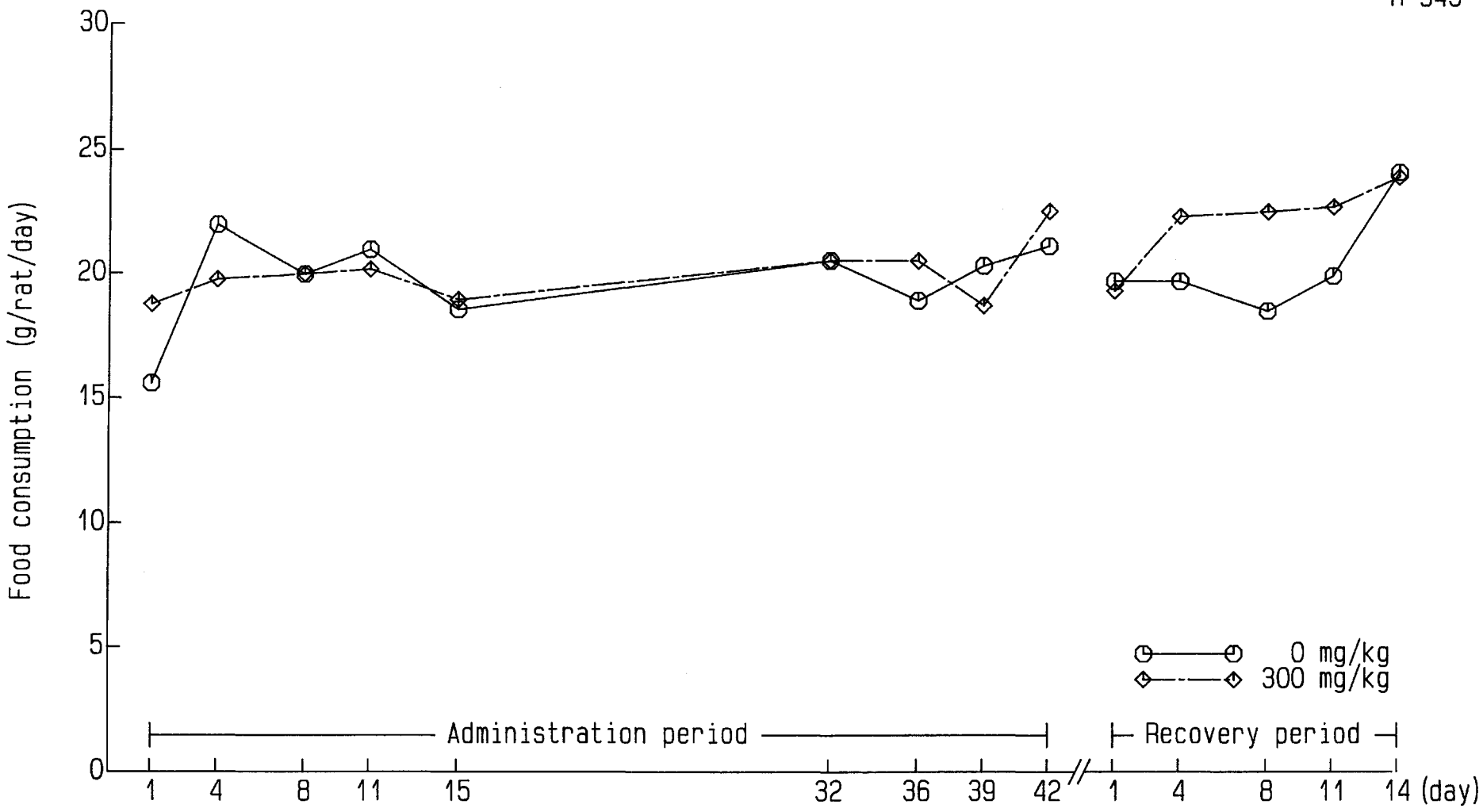

Fig.14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid, 4-hydroxy-, tin (2+) salt

Food consumption of female rats (Recovery group)

Table 1-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in male rats (Main group)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
12	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
60	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	0	0	0
300	No. of animals	12	12	12	12	12	12
	No. of animals with abnormal findings	0	0	0	2	4	4
	Salivation	0	0	0	2	4	4

Table 1-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in female rats during the pre-mating period (Main group)

Dose mg/kg	Signs	Administration														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a)
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
12	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
60	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
300	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

a): Day of administration

Table 1-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

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	22a)
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	6	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	
12	No. of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6	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	
60	No. of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	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	
300	No. of dams	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	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	

a): Day of gestation

Table 1-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in dams during the lactation period (Main group)

Dose mg/kg	Signs	Administration 0	1	2	3	4a)
0	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
12	No. of dams	11	11	11	11	11
	No. of dams with abnormal findings	0	0	0	0	0
60	No. of dams	12	12	12	12	12
	No. of dams with abnormal findings	0	0	0	0	0
300	No. of dams	10	10	10	10	10
	No. of dams with abnormal findings	0	0	0	0	0

a): Day of lactation

Table 1-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in male rats (Recovery group, administration period)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0
300	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0

Table 1-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in female rats (Recovery group, administration period)

Dose mg/kg	Signs	Day of administration					
		1-7	8-14	15-21	22-28	29-35	36-42
0	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0
300	No. of animals	5	5	5	5	5	5
	No. of animals with abnormal findings	0	0	0	0	0	0

Table 1-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in male rats (Recovery group, recovery period)

Dose mg/kg	Signs	Day of recovery													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	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
300	No. of animals	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

Table 1-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Clinical signs in female rats (Recovery group, recovery period)

Dose mg/kg	Signs	Day of recovery													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	No. of animals	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
300	No. of animals	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

Table 2-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 1 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 2 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 3 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 4 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 5 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Main group, Week 6 of administration)

	Dose (mg/kg)	0	12	60	300
Parameter	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 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 12
Posture					
Normal		12	12	12	12
Convulsion					
None		12	12	12	12
Abnormal behavior					
None		12	12	12	12

Table 2-9 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 7 of copulation)

	Dose (mg/kg)	12
Parameter	No. of animals	1
Posture		
Normal		1
Convulsion		
None		1
Abnormal behavior		
None		1

Table 2-10 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 1 of gestation)

	Dose (mg/kg)	0	12	60	300
Parameter	No. of animals	12	11	12	10
Posture					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10

Table 2-11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 7 of gestation)

	Dose (mg/kg)	0	12	60	300
Parameter	No. of animals	12	11	12	10
Posture					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10

Table 2-12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 14 of gestation)

	Dose (mg/kg)	0	12	60	300
Parameter	No. of animals	12	11	12	10
Posture					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10

Table 2-13 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 20 of gestation)

	Dose (mg/kg)	0	12	60	300
Parameter	No. of animals	12	11	12	10
Posture					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10

Table 2-14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Main group, Day 4 of lactation)

	Dose (mg/kg)	0	12	60	300
Parameter	No. of animals	12	11	12	10
Posture					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10

Table 2-15 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 1 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-16 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 2 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-17 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 3 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-18 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 4 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-19 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 5 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-20 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 6 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-21 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg)	0	300
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-22 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: home cage observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-23 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0	300
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-24 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 2 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-25 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 3 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-26 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	300
	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-27 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 5 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-28 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 6 of administration)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-29 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 1 of recovery)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-30 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: home cage observations (Recovery group, Week 2 of recovery)

	Dose (mg/kg)	0	300
Parameter	No. of animals	5	5
Posture			
Normal		5	5
Convulsion			
None		5	5
Abnormal behavior			
None		5	5

Table 2-31 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 12
Ease of removal from cage					
	Easy	12	11	11	12
	Some resistance/avoidance	0	1	1	0
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	10	9	9
	Soft	2	2	3	3
Reactivity to handling					
	Easy	12	12	12	12

Table 2-32 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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 2-33 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 3 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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	11
Soft		0	0	0	1
Reactivity to handling					
Easy		12	12	12	12

Table 2-34 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 4 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 12
Ease of removal from cage					
	Easy	12	11	10	11
	Some resistance/avoidance	0	1	2	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	11	9	10
	Soft	0	1	3	2
Reactivity to handling					
	Easy	11	12	12	12
	Slightly awkward	1	0	0	0

Table 2-35 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 5 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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	9	11
Soft		0	0	3	1
Reactivity to handling					
Easy		12	12	12	12

Table 2-36 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Main group, Week 6 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 12
Ease of removal from cage					
	Easy	12	11	11	11
	Some resistance/avoidance	0	1	1	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	11	10	10	10
	Soft	1	2	2	1
	Moderate	0	0	0	1
Reactivity to handling					
	Easy	12	11	11	11
	Slightly awkward	0	1	1	1

Table 2-37 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Week 1 of administration)

Dose (mg/kg)	0	12	60	300
Parameter No. of animals	12	12	12	12
Ease of removal from cage				
Easy	12	11	12	12
Some resistance/avoidance	0	1	0	0
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	11	12	11
Soft	0	1	0	1
Reactivity to handling				
Easy	12	12	12	12

Table 2-38 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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 2-39 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 7 of copulation)

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

Table 2-40 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 1 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Ease of removal from cage					
	Easy	12	11	12	10
Fur condition					
	Normal	12	11	12	10
Skin					
	Normal	12	11	12	10
Secretions-Eye, Nose					
	Absent	12	11	12	10
Exophthalmos					
	Absent	12	11	12	10
Palpebral closure					
	Normal	12	11	12	10
Mucosal membranes					
	Normal	12	11	12	10
Lacrimation					
	Normal	12	11	12	10
Piloerection					
	Absent	12	11	12	10
Pupil size					
	Normal	12	11	12	10
Salivation					
	None	12	11	12	10
Abnormal respiration					
	Absent	12	11	12	10
Vocalization					
	None	11	11	11	9
	Soft	1	0	1	1
Reactivity to handling					
	Easy	12	11	11	9
	Slightly awkward	0	0	1	1

Table 2-41 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 7 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Ease of removal from cage					
	Easy	12	11	12	9
	Some resistance/avoidance	0	0	0	1
Fur condition					
	Normal	12	11	12	10
Skin					
	Normal	12	11	12	10
Secretions-Eye, Nose					
	Absent	12	11	12	10
Exophthalmos					
	Absent	12	11	12	10
Palpebral closure					
	Normal	12	11	12	10
Mucosal membranes					
	Normal	12	11	12	10
Lacrimation					
	Normal	12	11	12	10
Piloerection					
	Absent	12	11	12	10
Pupil size					
	Normal	12	11	12	10
Salivation					
	None	12	11	12	10
Abnormal respiration					
	Absent	12	11	12	10
Vocalization					
	None	11	11	11	8
	Soft	1	0	1	2
Reactivity to handling					
	Easy	11	11	12	9
	Slightly awkward	1	0	0	1

Table 2-42 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 14 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Ease of removal from cage					
Easy		12	11	12	10
Fur condition					
Normal		12	11	12	10
Skin					
Normal		12	11	12	10
Secretions-Eye, Nose					
Absent		12	11	12	10
Exophthalmos					
Absent		12	11	12	10
Palpebral closure					
Normal		12	11	12	10
Mucosal membranes					
Normal		12	11	12	10
Lacrimation					
Normal		12	11	12	10
Piloerection					
Absent		12	11	12	10
Pupil size					
Normal		12	11	12	10
Salivation					
None		12	11	12	10
Abnormal respiration					
Absent		12	11	12	10
Vocalization					
None		12	11	12	10
Reactivity to handling					
Easy		12	11	12	10

Table 2-43 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 20 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Ease of removal from cage					
	Easy	12	10	12	10
	Some resistance/avoidance	0	1	0	0
Fur condition					
	Normal	12	11	12	10
Skin					
	Normal	12	11	12	10
Secretions-Eye, Nose					
	Absent	12	11	12	10
Exophthalmos					
	Absent	12	11	12	10
Palpebral closure					
	Normal	12	11	12	10
Mucosal membranes					
	Normal	12	11	12	10
Lacrimation					
	Normal	12	11	12	10
Piloerection					
	Absent	12	11	12	10
Pupil size					
	Normal	12	11	12	10
Salivation					
	None	12	11	12	10
Abnormal respiration					
	Absent	12	11	12	10
Vocalization					
	None	11	10	12	9
	Soft	1	0	0	1
	Moderate	0	1	0	0
Reactivity to handling					
	Easy	12	9	12	9
	Slightly awkward	0	2	0	1

Table 2-44 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Main group, Day 4 of lactation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Ease of removal from cage					
	Easy	12	11	12	10
Fur condition					
	Normal	12	11	12	10
Skin					
	Normal	12	11	12	10
Secretions-Eye, Nose					
	Absent	12	11	12	10
Exophthalmos					
	Absent	12	11	12	10
Palpebral closure					
	Normal	12	11	12	10
Mucosal membranes					
	Normal	12	11	12	10
Lacrimation					
	Normal	12	11	12	10
Piloerection					
	Absent	12	11	12	10
Pupil size					
	Normal	12	11	12	10
Salivation					
	None	12	11	12	10
Abnormal respiration					
	Absent	12	11	12	10
Vocalization					
	None	12	11	12	9
	Soft	0	0	0	1
Reactivity to handling					
	Easy	12	11	12	10

Table 2-45 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 1 of administration)

Dose (mg/kg)	0	300
Parameter 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	4	5
Soft	1	0
Reactivity to handling		
Easy	5	5

Table 2-46 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg)	0	300
	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		4	5
Soft		1	0
Reactivity to handling			
Easy		5	5

Table 2-47 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 3 of administration)

Dose (mg/kg)	0	300
Parameter 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 2-48 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	300
	No. of animals	5	5
Ease of removal from cage			
Easy		4	5
Some resistance/avoidance		1	0
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		4	5
Soft		1	0
Reactivity to handling			
Easy		5	5

Table 2-49 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	300
	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 2-50 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	300
	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 2-51 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-52 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: in-the-hand observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	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		4	5
Soft		1	0
Reactivity to handling			
Easy		5	5

Table 2-53 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-54 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-55 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 3 of administration)

Dose (mg/kg)	0	300
Parameter / No. of animals	5	5
Ease of removal from cage		
Easy	5	3
Some resistance/avoidance	0	2
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	2
Slightly awkward	0	3

Table 2-56 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	300
	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		4	3
Soft		1	2
Reactivity to handling			
Easy		5	4
Slightly awkward		0	1

Table 2-57 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-58 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-59 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-60 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: in-the-hand observations (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-61 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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	4± 2	3± 2	5± 3
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 1	0± 1
Urination					
None		12	12	11	12
Small amount		0	0	1	0

No significant difference in any treated groups from control group.

Table 2-62 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		2± 2	3± 2	3± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	10	12	10
Small amount		1	2	0	2

No significant difference in any treated groups from control group.

Table 2-63 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 3 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		4± 2	4± 2	3± 2	4± 3
Defecation count (Mean±S.D.)		0± 1	0± 0	0± 1	0± 0
Urination					
	None	12	9	12	9
	Small amount	0	3	0	3

No significant difference in any treated groups from control group.

Table 2-64 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 4 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		4± 2	4± 2	4± 2	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 1	0± 0
Urination					
None		10	10	11	9
Small amount		2	2	1	3

No significant difference in any treated groups from control group.

Table 2-65 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 5 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		4± 1	3± 2	4± 2	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
	None	11	10	10	10
	Small amount	1	2	2	2

No significant difference in any treated groups from control group.

Table 2-66 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Main group, Week 6 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		4± 2	5± 2	5± 2	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	8	8	10
Small amount		1	4	4	2

No significant difference in any treated groups from control group.

Table 2-67 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		6± 1	5± 2	5± 1	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 1
Urination					
	None	12	12	12	12

No significant difference in any treated groups from control group.

Table 2-68 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 12	60 12	300 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.)		6± 1	6± 2	5± 2	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 2-69 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 7 of copulation)

Parameter	Dose (mg/kg) / No. of animals	12 1
Arousal		
Normal		1
Convulsion		
None		1
Abnormal behavior		
None		1
Stereotypy		
None		1
Gait		
Normal		1
Posture		
Normal		1
Grooming		
None		1
Rearing (Mean±S.D.)		7± 0
Defecation count (Mean±S.D.)		0± 0
Urination		
None		1

Table 2-70 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 1 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Arousal					
	Normal	12	11	12	10
Convulsion					
	None	12	11	12	10
Abnormal behavior					
	None	12	11	12	10
Stereotypy					
	None	12	11	12	10
Gait					
	Normal	12	11	12	10
Posture					
	Normal	12	11	12	10
Grooming					
	None	12	11	12	10
Rearing (Mean±S.D.)		6± 2	6± 2	6± 3	7± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
	None	12	11	12	10

No significant difference in any treated groups from control group.

Table 2-71 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 7 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Arousal					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10
Stereotypy					
None		12	11	12	10
Gait					
Normal		12	11	12	10
Posture					
Normal		12	11	12	10
Grooming					
None		12	11	12	10
Rearing (Mean±S.D.)		6± 2	6± 1	7± 2	7± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	10	11	10
Small amount		1	1	1	0

No significant difference in any treated groups from control group.

Table 2-72 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 14 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Arousal					
	Normal	12	11	12	10
Convulsion					
	None	12	11	12	10
Abnormal behavior					
	None	12	11	12	10
Stereotypy					
	None	12	11	12	10
Gait					
	Normal	12	11	12	10
Posture					
	Normal	12	11	12	10
Grooming					
	None	12	11	12	10
Rearing (Mean±S.D.)		6± 2	6± 2	6± 2	7± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
	None	12	11	12	10

No significant difference in any treated groups from control group.

Table 2-73 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 20 of gestation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Arousal					
Normal		12	11	12	10
Convulsion					
None		12	11	12	10
Abnormal behavior					
None		12	11	12	10
Stereotypy					
None		12	11	12	10
Gait					
Normal		12	11	12	10
Posture					
Normal		12	11	12	10
Grooming					
None		12	11	12	10
Rearing (Mean±S.D.)		6± 1	6± 2	6± 2	7± 1
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
None		11	10	12	10
Small amount		1	1	0	0

No significant difference in any treated groups from control group.

Table 2-74 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Main group, Day 4 of lactation)

Parameter	Dose (mg/kg) / No. of animals	0 12	12 11	60 12	300 10
Arousal					
	Normal	12	11	12	10
Convulsion					
	None	12	11	12	10
Abnormal behavior					
	None	12	11	12	10
Stereotypy					
	None	12	11	12	10
Gait					
	Normal	12	11	12	10
Posture					
	Normal	12	11	12	10
Grooming					
	None	12	11	12	10
Rearing (Mean±S.D.)		6± 1	7± 2	8± 2	6± 2
Defecation count (Mean±S.D.)		0± 0	0± 0	0± 0	0± 0
Urination					
	None	11	11	12	10
	Small amount	1	0	0	0

No significant difference in any treated groups from control group.

Table 2-75 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		4± 2	4± 1
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 2-76 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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± 1	3± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
	None	4	5
	Small amount	1	0

No significant difference between treated group and control group.

Table 2-77 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 3 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		4± 1	4± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
	None	4	5
	Small amount	1	0

No significant difference between treated group and control group.

Table 2-78 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg)	0	300
	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.)		4± 1	4± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		4	5
Small amount		1	0

No significant difference between treated group and control group.

Table 2-79 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg)	0	300
	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.)		4± 1	4± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	3
Small amount		0	2

No significant difference between treated group and control group.

Table 2-80 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		6± 2	5± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
	None	5	4
	Moderate amount	0	1

No significant difference between treated group and control group.

Table 2-81 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg)	0	300
	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± 1	5± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		3	4
Small amount		2	0
Moderate amount		0	1

No significant difference between treated group and control group.

Table 2-82 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in male rats: open field observation (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	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± 1	5± 1
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 2-83 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 1 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 / 5	300 / 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± 2	5± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
	None	5	5

No significant difference between treated group and control group.

Table 2-84 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 2 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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 2-85 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 3 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		8± 2	9± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
	None	5	5

No significant difference between treated group and control group.

Table 2-86 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 4 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		8± 2	8± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-87 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 5 of administration)

Parameter	Dose (mg/kg) / No. of animals	0 5	300 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.)		9± 3	9± 1
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-88 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 6 of administration)

Dose (mg/kg)	0	300
Parameter 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.)	9± 4	8± 3
Defecation count (Mean±S.D.)	0± 0	0± 0
Urination		
None	5	5

No significant difference between treated group and control group.

Table 2-89 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 1 of recovery)

Parameter	Dose (mg/kg)	0	300
	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.)		9± 3	9± 3
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-90 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Detailed clinical signs in female rats: open field observation (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	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.)		9± 3	8± 2
Defecation count (Mean±S.D.)		0± 0	0± 0
Urination			
None		5	5

No significant difference between treated group and control group.

Table 2-91 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of male rats (Main group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	12	60	300
	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.)		87± 9	66±16	74±14	78±20

No significant difference in any treated groups from control group.

Table 2-92 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of female rats (Main group, Day 4 of lactation)

Parameter	Dose (mg/kg) / No. of animals	0 5	12 5	60 5	300 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.)		74±15	63± 8	55±13	53±13*D

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

Table 2-93 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of male rats (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	300
	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.)		87±10	73±17

No significant difference between treated group and control group.

Table 2-94 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of female rats (Recovery group, Week 6 of administration)

Parameter	Dose (mg/kg)	0	300
	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.)		59± 9	67±20

No significant difference between treated group and control group.

Table 2-95 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of male rats (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	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.)		96±15	81±21

No significant difference between treated group and control group.

Table 2-96 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Manipulative test of female rats (Recovery group, Week 2 of recovery)

Parameter	Dose (mg/kg)	0	300
	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.)		67±16	75±14

No significant difference between treated group and control group.

Table 2-97 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of male rats (Main group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1480	957
	S.D.	186	145
12	No.	5	5
	Mean	1338	863
	S.D.	204	98
60	No.	5	5
	Mean	1529	912
	S.D.	244	221
300	No.	5	5
	Mean	1388	973
	S.D.	186	137

No significant difference in any treated groups from control group.

Table 2-98 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of female rats (Main group, Day 4 of lactation)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1347	767
	S.D.	145	60
12	No.	5	5
	Mean	1377	840
	S.D.	134	147
60	No.	5	5
	Mean	1178	723
	S.D.	88	109
300	No.	5	5
	Mean	1232	772
	S.D.	121	91

No significant difference in any treated groups from control group.

Table 2-99 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of male rats (Recovery group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1449	890
	S.D.	285	227
300	No.	5	5
	Mean	1196	746
	S.D.	210	136

No significant difference between treated group and control group.

Table 2-100 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of female rats (Recovery group, Week 6 of administration)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	975	758
	S.D.	151	110
300	No.	5	5
	Mean	948	662
	S.D.	92	177

No significant difference between treated group and control group.

Table 2-101 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of male rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1549	735
	S.D.	219	123
300	No.	5	5
	Mean	1304	787
	S.D.	169	214

No significant difference between treated group and control group.

Table 2-102 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Grip strength of female rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1216	792
	S.D.	175	139
300	No.	5	5
	Mean	1207	663
	S.D.	141	82

No significant difference between treated group and control group.

Table 2-103 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of male rats (Main 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	371	303	248	129	129	40	1220
	S.D.	41	138	91	116	119	34	405
12	No.	5	5	5	5	5	5	5
	Mean	423	389	154	43	142	81	1234
	S.D.	10	14	55	7	130	89	245
60	No.	5	5	5	5	5	5	5
	Mean	361	227	138	48	128	101	1003
	S.D.	96	106	119	77	112	104	433
300	No.	5	5	5	5	5	5	5
	Mean	383	236	179	71	153	32	1055
	S.D.	34	109	128	81	89	13	323

No significant difference in any treated groups from control group.

Table 2-104 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of female rats (Main group, Day 4 of lactation)

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	348	209	124	131	93	84	989
	S.D.	93	139	143	181	143	128	795
12	No.	5	5	5	5	5	5	5
	Mean	315	152	162	78	23	9	738
	S.D.	53	85	75	93	18	8	231
60	No.	5	5	5	5	5	5	5
	Mean	341	190	184	103	64	76	958
	S.D.	44	95	121	105	60	83	385
300	No.	5	5	5	5	5	5	5
	Mean	332	134	93	63	58	15	694
	S.D.	58	121	101	92	46	10	343

No significant difference in any treated groups from control group.

Table 2-105 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of male rats (Recovery 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	444	421	339	240	160	109	1714
	S.D.	16	46	72	150	148	150	493
300	No.	5	5	5	5	5	5	5
	Mean	403*	353*	209**	175	153	102	1396
	S.D.	37T	32T	46T	84	129	70	326

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

Table 2-106 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of female rats (Recovery 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	346	234	147	165	139	140	1172
	S.D.	62	127	91	105	134	91	522
300	No.	5	5	5	5	5	5	5
	Mean	370	270	201	150	255	220	1466
	S.D.	19	90	175	110	134	112	209

No significant difference between treated group and control group.

Table 2-107 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of male rats (Recovery group, 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	416	389	332	312	187	118	1753
	S.D.	22	28	86	150	136	159	462
300	No.	5	5	5	5	5	5	5
	Mean	409	390	298	310	339	238	1983
	S.D.	46	25	77	134	82	125	306

No significant difference between treated group and control group.

Table 2-108 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Motor activity of female rats (Recovery group, 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	329	235	239	207	169	176	1356
	S.D.	93	47	33	37	124	124	368
300	No.	5	5	5	5	5	5	5
	Mean	345	229	235	180	192	150	1330
	S.D.	52	87	66	93	124	100	307

No significant difference between treated group and control group.

Table 3-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of male rats (Main group)

Dose mg/kg		Pre-mating period					Mating period				Post-mating period				Gain 1-42
		1	4	8	11	15	18	22	25	29	32	36	39	42a)	
0	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	365.9	380.4	393.8	406.8	419.8	426.1	443.9	454.4	467.4	478.5	489.8	492.4	498.8	132.8
	S.D.	15.3	18.6	21.7	24.5	26.5	23.0	24.7	27.7	29.0	31.4	32.1	35.6	34.0	22.3
12	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	367.4	381.0	393.3	404.8	419.3	425.3	442.6	455.0	469.2	476.4	490.2	494.9	497.4	130.0
	S.D.	17.8	19.0	21.8	22.9	25.2	24.7	24.5	26.1	26.9	29.5	28.6	30.3	27.9	22.0
60	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	365.0	379.8	395.7	407.0	418.1	427.3	443.9	454.3	468.8	476.8	489.8	491.8	500.7	135.7
	S.D.	17.7	18.3	20.3	23.6	25.5	27.2	26.9	28.6	30.6	31.2	33.2	32.5	32.5	22.3
300	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	366.5	375.2	389.8	399.8	413.8	421.4	435.3	442.8	457.0	466.3	478.5	478.6	481.8	115.3
	S.D.	15.9	15.0	16.6	16.2	17.4	20.3	18.1	19.7	18.7	21.9	22.5	22.3	24.9	18.1

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

Table 3-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg		Administration 1	4	8	11	15a)	Gain 1-15
0	No.	12	12	12	12	12	12
	Mean	231.2	239.8	247.8	254.3	256.8	25.6
	S.D.	13.3	11.2	11.3	11.6	12.7	7.7
12	No.	12	12	12	12	12	12
	Mean	232.8	242.3	249.8	257.3	263.4	30.6
	S.D.	11.7	12.3	13.7	15.6	16.3	10.6
60	No.	12	12	12	12	12	12
	Mean	232.6	238.8	245.7	253.2	258.5	25.9
	S.D.	13.7	12.5	12.7	9.3	10.4	8.5
300	No.	12	12	12	12	12	12
	Mean	230.3	236.5	245.5	250.9	256.5	26.2
	S.D.	13.7	13.6	15.5	15.8	17.8	8.4

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

Table 3-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of dams during the gestation period (Main group)

Dose mg/kg		Administration 0	4	7	11	14	17	20a)	Gain 0-20
0	No.	12	12	12	12	12	12	12	12
	Mean	266.2	285.1	297.9	319.3	331.1	362.7	409.1	142.9
	S.D.	13.5	14.2	15.2	17.0	16.8	19.1	25.9	27.6
12	No.	11	11	11	11	11	11	11	11
	Mean	268.6	291.2	303.6	324.9	339.6	368.3	418.4	149.7
	S.D.	14.1	15.7	16.5	16.4	16.3	17.3	17.7	14.9
60	No.	12	12	12	12	12	12	12	12
	Mean	264.6	287.8	300.9	322.1	337.1	368.1	416.4	151.8
	S.D.	13.6	12.7	12.6	14.5	14.0	12.6	12.0	11.4
300	No.	10	10	10	10	10	10	10	10
	Mean	263.3	284.5	296.8	317.2	333.4	363.0	408.1	144.8
	S.D.	18.9	21.1	20.0	26.6	24.3	23.0	24.3	13.1

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

Table 3-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of dams during the lactation period (Main group)

Dose mg/kg		Administration 0	Administration 4a)	Gain 0-4
0	No.	12	12	12
	Mean	324.3	333.8	9.5
	S.D.	19.8	15.1	14.1
12	No.	11	11	11
	Mean	326.8	339.5	12.7
	S.D.	20.1	15.7	16.3
60	No.	12	12	12
	Mean	326.3	342.1	15.8
	S.D.	19.5	15.1	12.6
300	No.	10	10	10
	Mean	320.4	338.3	17.9
	S.D.	29.8	28.9	17.3

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

Table 3-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of male rats during the administration period (Recovery group)

Dose mg/kg		Day of administration 1	4	8	11	15	18	22	25	29	32	36	39	42	Gain 1-42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	369.2	383.4	397.8	412.0	426.6	435.0	452.0	460.6	473.2	485.0	497.2	492.8	500.2	131.0
	S.D.	22.5	21.9	22.7	25.6	26.5	28.6	29.3	30.4	34.4	35.2	36.3	35.8	42.0	22.0
300	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	362.8	373.2	388.2	398.6	412.6	420.0	434.6	444.2	458.0	462.8	475.4	477.4	482.0	119.2
	S.D.	12.8	15.0	11.8	16.1	18.6	19.5	26.4	24.9	26.3	27.7	27.6	27.4	30.7	21.4

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

Table 3-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of female rats during the administration period (Recovery group)

Dose mg/kg		Day of administration 1	4	8	11	15	18	22	25	29	32	36	39	42	Gain 1-42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	228.8	238.0	246.2	252.4	258.6	262.2	265.8	276.0	278.8	278.8	283.2	286.8	289.0	60.2
	S.D.	13.2	14.5	13.9	12.0	15.8	18.0	15.2	23.7	23.4	17.5	18.5	27.5	24.1	15.5
300	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	231.6	237.4	246.0	249.0	254.4	261.2	265.0	264.4	271.4	276.6	283.8	281.6	285.2	53.6
	S.D.	13.4	10.5	12.4	17.0	14.9	16.7	10.5	16.4	18.9	15.9	14.6	11.2	14.9	9.8

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

Table 3-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of male rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery 1	4	8	11	14	Gain 1-14
0	No.	5	5	5	5	5	5
	Mean	504.8	511.0	523.2	520.2	527.6	22.8
	S.D.	46.9	46.3	49.1	48.0	50.4	4.9
300	No.	5	5	5	5	5	5
	Mean	486.4	491.2	501.8	507.4	518.4	32.0
	S.D.	30.5	30.5	32.7	29.8	29.9	7.8

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

Table 3-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of female rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery 1	4	8	11	14	Gain 1-14
0	No.	5	5	5	5	5	5
	Mean	289.8	290.0	295.0	295.6	301.2	11.4
	S.D.	23.2	23.2	20.4	23.7	22.5	3.8
300	No.	5	5	5	5	5	5
	Mean	284.6	285.0	294.2	294.6	299.4	14.8
	S.D.	7.8	17.0	18.9	18.1	18.7	11.8

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

Table 4-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of male rats (Main group)

Dose mg/kg		Pre-mating period					Post-mating period			
		1	4	8	11	15	32	36	39	42a)
0	No.	12	12	12	12	12	12	12	12	12
	Mean	26.2	28.7	26.9	28.8	26.3	31.3	28.1	29.1	32.9
	S.D.	2.4	2.0	2.2	2.9	1.9	1.8	2.8	3.7	4.0
12	No.	12	12	12	12	12	12	12	12	12
	Mean	25.8	28.6	26.1	27.9	26.4	32.3	29.4	30.5	31.1
	S.D.	1.8	2.2	3.3	1.2	1.6	2.3	1.8	2.5	3.1
60	No.	12	12	12	12	12	12	12	12	12
	Mean	24.3	28.7	26.8	28.2	25.3	30.2	27.7	28.8	32.1
	S.D.	2.0	1.9	2.1	2.2	2.1	1.3	2.5	1.8	2.9
300	No.	12	12	12	12	12	12	12	12	12
	Mean	27.0	27.1	28.2	26.3	27.3	31.1	29.3	29.3	30.8
	S.D.	2.5	3.1	3.0	5.1	3.1	3.3	2.7	2.3	3.2

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

Table 4-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of female rats during the pre-mating period (Main group)

Dose mg/kg		Administration 1	4	8	11	15a)
0	No.	12	12	12	12	12
	Mean	17.3	21.7	20.3	20.3	19.5
	S.D.	3.7	1.4	2.2	2.6	2.2
12	No.	12	12	12	12	12
	Mean	16.7	20.8	19.8	21.6	20.4
	S.D.	3.7	2.7	2.2	2.3	1.9
60	No.	12	12	12	12	12
	Mean	17.9	20.6	19.1	20.3	19.1
	S.D.	1.6	2.5	2.2	2.9	2.7
300	No.	12	12	12	12	12
	Mean	17.3	19.6	19.2	19.8	20.2
	S.D.	3.3	2.2	2.1	3.2	3.1

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

Table 4-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of dams during the gestation period (Main group)

Dose mg/kg		Administration 1	4	7	11	14	17	20a)
0	No.	12	12	12	12	12	12	12
	Mean	21.3	24.3	25.7	27.0	25.3	29.4	23.9
	S.D.	3.3	1.7	3.4	2.6	2.3	2.7	2.9
12	No.	11	11	11	11	11	11	11
	Mean	21.5	26.0	26.0	28.0	26.0	27.6	25.0
	S.D.	3.6	2.9	2.2	3.0	2.0	2.6	2.1
60	No.	12	12	12	12	12	12	12
	Mean	22.0	24.7	26.0	27.1	25.9	28.3	24.0
	S.D.	2.3	2.0	2.3	1.7	2.2	2.7	2.2
300	No.	10	10	10	10	10	10	10
	Mean	21.8	24.8	25.9	26.1	24.4	27.9	22.7
	S.D.	1.5	3.5	3.1	3.9	2.7	3.1	2.9

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

Table 4-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of dams during the lactation period (Main group)

Dose mg/kg		Administration 2	4a)
0	No.	12	12
	Mean	22.8	42.9
	S.D.	6.4	6.8
12	No.	11	11
	Mean	25.5	42.7
	S.D.	5.2	5.3
60	No.	12	12
	Mean	26.2	45.0
	S.D.	4.3	3.1
300	No.	10	10
	Mean	28.4	44.7
	S.D.	7.7	3.9

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

Table 4-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of male rats during the administration period (Recovery group)

Dose mg/kg		Day of administration								
		1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5
	Mean	27.4	29.6	26.6	29.4	27.4	30.6	29.2	28.4	31.6
	S.D.	5.0	2.7	3.2	3.1	4.0	3.1	3.6	2.3	3.8
300	No.	5	5	5	5	5	5	5	5	5
	Mean	24.6	26.6	28.0	28.4	27.6	29.2	28.2	32.4*	31.8
	S.D.	2.3	2.3	2.2	2.3	4.0	2.3	1.6	0.9AT	2.2

Unit: g/rat/day
No.: No. of animals
*: $p<0.05$ (Significant difference from control group)
AT: Aspin-Welch t-test

Table 4-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of female rats during the administration period (Recovery group)

Dose mg/kg		Day of administration								
		1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5
	Mean	15.6	22.0	20.0	21.0	18.6	20.6	19.0	20.4	21.2
	S.D.	4.2	1.2	2.1	1.7	3.1	1.9	3.7	5.0	4.0
300	No.	5	5	5	5	5	5	5	5	5
	Mean	18.8	19.8*	20.0	20.2	19.0	20.6	20.6	18.8	22.6
	S.D.	3.6	1.1T	2.0	4.1	3.3	1.9	3.0	1.6	4.2

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

Table 4-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of male rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery 1	4	8	11	14
0	No.	5	5	5	5	5
	Mean	28.6	29.0	30.8	29.8	31.6
	S.D.	3.0	3.4	4.3	2.7	2.5
300	No.	5	5	5	5	5
	Mean	29.0	30.2	29.6	30.4	32.6
	S.D.	4.6	3.3	3.0	2.2	1.1

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

Table 4-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Food consumption of female rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery 1	4	8	11	14
0	No.	5	5	5	5	5
	Mean	19.8	19.8	18.6	20.0	24.2
	S.D.	3.2	2.2	4.2	3.4	3.2
300	No.	5	5	5	5	5
	Mean	19.4	22.4	22.6	22.8	24.0
	S.D.	4.0	5.3	3.7	4.3	2.9

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

Table 5-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	pH									1) Protein						2) Ketone body						3) Glucose					
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++	-	+-	+	++	+++	++++
0	17	0	0	0	1	2	1	3	9	1	3	6	8	0	0	0	9	5	3	0	0	0	17	0	0	0	0	0
12	12	0	0	0	0	4	1	2	5	0	0	8	4	0	0	0	6	5	1	0	0	0	12	0	0	0	0	0
60	12	0	0	0	4	3	0	5	0	0	1	3	8	0	0	0	4	4	4	0	0	0	12	0	0	0	0	0
300	17	0	0	0	6	5	2	3	0	1	0	1	16	0	0	0	0	5	12	0	0	0	17	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
		-	+-	+	++	+++	-	+	++	+++	++++	+-	+	++	+++	++++	LY	Y	DY
0	17	16	1	0	0	0	17	0	0	0	0	16	1	0	0	0	0	17	0
12	12	9	3	0	0	0	12	0	0	0	0	12	0	0	0	0	0	12	0
60	12	11	1	0	0	0	12	0	0	0	0	11	1	0	0	0	0	12	0
300	17	16	0	0	1	0	16	1	0	0	0	12	5	0	0	0	0	17	0

4) - : <0.03 mg/dL +- : 0.03 - 0.05 mg/dL + : 0.06 - 0.15 mg/dL ++ : 0.16 - 0.75 mg/dL +++ : >0.75 mg/dL
5) - : <0.5 mg/dL + : 0.5 - 1.5 mg/dL ++ : 1.6 - 5.0 mg/dL +++ : 5.1 - 10.0 mg/dL ++++ : >10.0 mg/dL
6) +- : <2.0 mg/dL + : 2.0 - 3.5 mg/dL ++ : 3.6 - 7.0 mg/dL +++ : 7.1 - 12.0 mg/dL ++++ : >12.0 mg/dL
7) LY : Light yellow Y : Yellow DY : Dark yellow

Table 5-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	URINE SEDIMENT																																	
		RBC					WBC					SEC					SREC					Cast			CRYSTALLIZATION PS					CRYSTALLIZATION CO				
		-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	++	+++	-	+-	+	-	+-	+	++	+++	-	+-	+	++	+++
0	17	17	0	0	0	0	16	1	0	0	0	0	17	0	0	0	17	0	0	0	0	17	0	0	4	12	1	0	0	17	0	0	0	0
12	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	5	6	1	0	0	12	0	0	0	0
60	12	12	0	0	0	0	12	0	0	0	0	0	12	0	0	0	12	0	0	0	0	12	0	0	5	7	0	0	0	12	0	0	0	0
300	17	17	0	0	0	0	17	0	0	0	0	0	17	0	0	0	17	0	0	0	0	17	0	0	6	11	0	0	0	17	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

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Water intake and urinalysis (Week 6 of administration)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	17	Mean	45	18.9	1860
		S.D.	7	5.8	346
12	12	Mean	46	16.3	1960
		S.D.	5	5.3	361
60	12	Mean	42	14.8	2194*
		S.D.	8	7.8	461D
300	17	Mean	44	14.9	2129
		S.D.	7	2.9	257

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

Table 5-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	pH									1) Protein						2) Ketone body						3) Glucose					
		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	3	2	0	0	0	1	3	1	0	0	1	2	2	0	0	0	5	0	0	0	0	0
300	5	0	0	0	1	0	3	1	0	0	0	1	4	0	0	0	0	1	4	0	0	0	5	0	0	0	0	0

1) - : <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) - : <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) - : <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL

Table 5-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Urinalysis of male rats (Week 2 of recovery)

Dose mg/kg	No.	4) Occult blood					5) Bilirubin					6) Urobilinogen					7) Color		
		-	+-	+	++	+++	-	+	++	+++	++++	+-	+	++	+++	++++	LY	Y	DY
0	5	3	1	0	0	1	5	0	0	0	0	4	1	0	0	0	0	5	0
300	5	5	0	0	0	0	5	0	0	0	0	3	2	0	0	0	0	5	0

4) - : <0.03 mg/dL +- : 0.03 - 0.05 mg/dL + : 0.06 - 0.15 mg/dL ++ : 0.16 - 0.75 mg/dL +++ : >0.75 mg/dL
5) - : <0.5 mg/dL + : 0.5 - 1.5 mg/dL ++ : 1.6 - 5.0 mg/dL +++ : 5.1 - 10.0 mg/dL ++++ : >10.0 mg/dL
6) +- : <2.0 mg/dL + : 2.0 - 3.5 mg/dL ++ : 3.6 - 7.0 mg/dL +++ : 7.1 - 12.0 mg/dL ++++ : >12.0 mg/dL
7) LY : Light yellow Y : Yellow DY : Dark yellow

Table 5-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

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	3	1	0	1	0	5	0	0	0	0	0	4	1	0	0	5	0	0	0	0	5	0	0	0	4	1	0	0	5	0	0	0	0
300	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

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

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

Table 5-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Water intake and urinalysis (Week 2 of recovery)

Male

Dose mg/kg	No.		Water intake mL/24h	Urine volume mL/24h	Osmolality mOsm/kg
0	5	Mean	42	16.8	1923
		S.D.	9	4.9	296
300	5	Mean	50	18.6	1885
		S.D.	7	4.6	330

No significant difference between treated group and control group.

Table 6-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	846	15.7	42.0	49.7	18.5	37.3	2.2	121.7	14.5	20.5	292
		S.D.	20	0.5	1.4	0.9	0.4	0.4	0.3	15.9	1.3	3.5	30
12	5	Mean	867	16.2	43.3	50.0	18.6	37.3	1.9	106.1	14.7	21.3	288
		S.D.	36	0.3	1.0	1.1	0.5	0.3	0.3	12.8	1.8	2.9	38
60	5	Mean	871	16.4*	43.6	50.0	18.8	37.6	1.9	108.7	14.4	20.9	275
		S.D.	30	0.3D	1.4	0.5	0.5	0.8	0.4	7.2	0.9	1.6	17
300	5	Mean	872	15.5	42.1	48.2	17.7*	36.9	1.9	119.3	13.9	19.5	268
		S.D.	33	0.5	1.1	1.5	0.4D	0.5	0.1	14.7	0.8	3.3	21

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

Table 6-2

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Week 6 of administration)

Male

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)						Differential leukocyte counts ($X10^2/\mu L$)					
			$X10^2/\mu L$	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	78.6	72.5	22.6	1.5	0.3	2.6	0.5	58.9	15.9	1.1	0.2	2.0	0.4
		S.D.	30.9	8.5	8.0	1.0	0.2	0.5	0.2	29.4	2.9	0.6	0.2	0.7	0.2
12	5	Mean	88.2	79.3	15.6	1.6	0.2	2.4	0.9	69.7	14.1	1.4	0.2	2.1	0.7
		S.D.	21.1	5.4	6.2	0.5	0.0	0.4	0.6	16.4	8.4	0.2	0.1	0.4	0.5
60	5	Mean	102.1	79.0	17.3	0.9	0.3	2.1	0.4	80.5	17.9	0.9	0.3	2.1	0.5
		S.D.	26.8	5.4	5.8	0.2	0.1	0.6	0.1	22.1	7.3	0.3	0.1	0.7	0.2
300	5	Mean	89.4	75.3	20.0	1.5	0.2	2.3	0.7	68.8	16.6	1.1	0.2	2.1	0.7
		S.D.	33.1	7.2	6.4	0.8	0.1	0.4	0.3	29.2	4.2	0.5	0.2	0.9	0.6

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

Table 6-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	700	13.7	37.1	53.1	19.5	36.8	5.7	152.2	11.9	15.3	311
		S.D.	26	0.3	0.9	1.0	0.5	0.5	1.3	16.8	0.6	2.9	67
12	5	Mean	701	13.6	37.1	52.9	19.3	36.6	5.5	140.4	11.8	15.5	337
		S.D.	53	0.8	2.1	1.5	0.5	0.2	0.9	22.2	0.8	1.6	95
60	5	Mean	686	13.6	37.3	54.5	19.8	36.4	7.5	148.1	12.2	17.3	257
		S.D.	47	0.7	1.1	2.3	0.5	1.0	1.8	15.4	0.7	2.6	28
300	5	Mean	663	12.4*	34.3*	51.8	18.8	36.3	6.6	145.1	11.9	15.6	242
		S.D.	35	0.5D	0.9D	3.3	1.2	0.5	1.2	18.9	0.4	2.0	18

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

Table 6-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 4 of lactation)

Female

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)						Differential leukocyte counts ($X10^2/\mu L$)					
			$X10^2/\mu L$	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	116.0	56.8	39.1	1.0	0.2	2.2	0.7	64.7	46.6	1.0	0.2	2.6	0.8
		S.D.	30.0	7.2	7.8	0.6	0.1	0.7	0.2	13.3	18.4	0.3	0.1	1.2	0.2
12	5	Mean	141.9	59.6	36.6	0.8	0.2	2.3	0.6	83.2	53.3	1.0	0.3	3.2	0.8
		S.D.	43.5	7.0	6.7	0.6	0.0	0.4	0.2	22.0	23.6	0.5	0.1	1.2	0.5
60	5	Mean	143.3	53.0	42.3	0.9	0.2	3.0	0.6	75.4	61.2	1.3	0.2	4.3	0.9
		S.D.	36.2	5.0	5.3	0.4	0.1	0.5	0.4	18.1	19.3	0.4	0.1	1.4	0.5
300	5	Mean	120.0	61.4	34.0	0.8	0.2	3.0	0.6	74.1	40.4	1.0	0.2	3.6	0.7
		S.D.	27.7	3.9	3.9	0.3	0.1	0.8	0.1	20.0	7.7	0.3	0.1	1.4	0.3

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

Table 6-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	892	16.1	42.6	47.9	18.1	37.8	2.0	108.7	14.5	22.1	307
		S.D.	30	0.4	0.8	1.6	0.8	0.5	0.2	6.6	0.6	2.3	54
300	5	Mean	906	16.0	42.2	46.6	17.6	37.8	2.0	109.5	13.9	21.0	355
		S.D.	24	0.8	1.9	1.2	0.5	0.6	0.2	13.3	0.4	3.6	143

No significant difference between treated group and control group.

Table 6-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 14 of recovery)

Male

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)						Differential leukocyte counts ($\times10^2/\mu L$)					
			$\times10^2/\mu L$	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	118.1	80.6	14.6	1.3	0.3	2.2	0.9	96.4	16.0	1.5	0.4	2.6	1.1
		S.D.	31.1	5.9	5.7	0.2	0.1	0.7	0.3	30.3	2.2	0.3	0.2	1.1	0.4
300	5	Mean	131.3	77.7	17.4	1.3	0.4	2.1	1.1	102.5	22.4	1.6	0.6	2.7	1.6
		S.D.	43.7	8.7	8.9	0.6	0.2	0.8	0.6	35.3	11.8	0.6	0.5	1.0	1.5

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

Table 6-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 14 of recovery)

Female

Dose mg/kg	No.		RBC $\times10^4/\mu L$	Hb g/dL	Ht %	MCV fL	MCH pg	MCHC g/dL	Reticulocyte %	Platelet $\times10^4/\mu L$	PT s	APTT s	Fibrinogen mg/dL
0	5	Mean	812	15.5	40.6	50.0	19.1	38.2	2.0	114.3	12.6	17.0	211
		S.D.	18	0.3	0.5	1.3	0.3	0.7	0.2	7.6	0.6	2.3	10
300	5	Mean	846	16.3*	42.7*	50.5	19.3	38.3	1.6*	121.8	12.4	17.6	204
		S.D.	34	0.6T	1.6AT	1.7	0.4	0.5	0.2T	13.2	0.4	1.4	18

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

Table 6-8

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Hematology (Day 14 of recovery)

Female

Dose mg/kg	No.		WBC	Differential leukocyte counts (%)						Differential leukocyte counts ($X10^2/\mu L$)					
			$X10^2/\mu L$	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC	Lymph.	Neut.	Eosino.	Baso.	Mono.	LUC
0	5	Mean	61.5	75.2	20.0	1.6	0.2	2.3	0.6	46.2	12.3	1.0	0.1	1.5	0.4
		S.D.	13.8	6.4	7.0	0.5	0.0	0.7	0.3	10.2	5.4	0.3	0.1	0.6	0.2
300	5	Mean	70.2	74.6	20.6	1.7	0.2	2.2	0.7	52.9	13.9	1.2	0.2	1.5	0.5
		S.D.	20.4	6.7	6.4	0.5	0.1	0.7	0.2	17.0	3.9	0.6	0.0	0.8	0.2

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

Table 7-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili-rubin mg/dL	Glucose mg/dL	BUN mg/dL	Crea-tinine mg/dL
0	5	Mean	75	31	63	0	390	43	18	80	0.1	133	13	0.29
		S.D.	13	5	10	1	44	6	5	9	0.0	13	2	0.05
12	5	Mean	67	30	51	1	433	41	33*	81	0.1	149	14	0.30
		S.D.	7	2	9	1	94	5	8D	8	0.0	14	1	0.03
60	5	Mean	65	26	54	1	400	35	22	71	0.1	138	13	0.28
		S.D.	6	3	14	1	87	9	8	9	0.0	10	2	0.04
300	5	Mean	75	45**	57	1	441	51	21	88	0.1	130	16	0.27
		S.D.	8	9D	13	0	109	7	10	8	0.0	10	2	0.03

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

Table 7-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Week 6 of administration)

Male

Dose mg/kg	No.		Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	143	4.8	108	9.3	6.1	5.9	2.6	0.81
		S.D.	1	0.2	2	0.3	0.9	0.2	0.1	0.06
12	5	Mean	142	4.9	107	9.5	6.5	6.0	2.6	0.78
		S.D.	1	0.5	2	0.2	0.2	0.1	0.1	0.05
60	5	Mean	142	4.8	108	9.5	6.4	6.1	2.7	0.76
		S.D.	1	0.4	1	0.1	0.5	0.2	0.1	0.03
300	5	Mean	141	5.1	107	9.3	6.4	5.9	2.7	0.83
		S.D.	1	0.2	2	0.1	0.4	0.1	0.1	0.05

No significant difference in any treated groups from control group.

Table 7-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili-rubin mg/dL	Glucose mg/dL	BUN mg/dL	Crea-tinine mg/dL
0	5	Mean	85	55	54	1	294	58	28	120	0.1	126	15	0.31
		S.D.	27	18	14	0	97	16	15	31	0.0	17	3	0.05
12	5	Mean	94	59	50	1	258	57	40	120	0.1	122	14	0.32
		S.D.	26	11	12	0	120	11	11	17	0.0	9	3	0.04
60	5	Mean	86	53	44	1	286	59	39	122	0.1	136	15	0.33
		S.D.	12	12	6	0	100	11	14	14	0.0	21	3	0.04
300	5	Mean	87	50	43	1	303	55	36	115	0.1	135	17	0.31
		S.D.	8	8	7	1	129	13	12	23	0.0	17	4	0.06

No significant difference in any treated groups from control group.

Table 7-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 4 of lactation)

Female

Dose mg/kg	No.		Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	140	4.6	107	10.0	7.1	6.5	2.9	0.79
		S.D.	2	0.7	2	0.2	0.6	0.3	0.2	0.03
12	5	Mean	140	4.8	109	10.0	7.1	6.4	2.9	0.84
		S.D.	1	0.3	1	0.4	1.0	0.1	0.1	0.03
60	5	Mean	140	4.3	107	9.7	7.3	6.3	2.9	0.82
		S.D.	2	0.7	2	0.2	1.6	0.2	0.2	0.04
300	5	Mean	141	4.4	107	9.8	7.3	5.9**	2.7	0.81
		S.D.	1	0.5	1	0.3	0.7	0.2D	0.2	0.03

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

Table 7-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili-rubin mg/dL	Glucose mg/dL	BUN mg/dL	Crea-tinine mg/dL
0	5	Mean	69	30	48	1	332	43	40	84	0.1	153	14	0.29
		S.D.	11	4	9	0	40	6	26	10	0.0	2	2	0.03
300	5	Mean	71	35	52	1	462*	41	38	80	0.1	149	16	0.29
		S.D.	16	11	13	0	77T	4	8	5	0.0	15	1	0.02

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

Table 7-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 14 of recovery)

Male

Dose mg/kg	No.		Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	142	4.7	106	9.5	6.0	6.1	2.6	0.76
		S.D.	1	0.2	2	0.2	0.6	0.1	0.0	0.04
300	5	Mean	142	4.7	107	9.7	6.4	6.1	2.6	0.74
		S.D.	1	0.4	3	0.2	0.5	0.2	0.3	0.10

No significant difference between treated group and control group.

Table 7-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.		AST (GOT) IU/L	ALT (GPT) IU/L	LDH IU/L	γ-GTP IU/L	AlP IU/L	T.cho mg/dL	TG mg/dL	PL mg/dL	T.bili-rubin mg/dL	Glucose mg/dL	BUN mg/dL	Crea-tinine mg/dL
0	5	Mean	61	25	44	1	170	65	11	128	0.1	141	16	0.40
		S.D.	6	5	8	0	49	7	4	13	0.0	9	3	0.03
300	5	Mean	70	30	44	1	257	61	11	122	0.1	132	17	0.35*
		S.D.	11	7	4	0	101	16	5	24	0.0	10	2	0.04T

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

Table 7-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Blood chemistry (Day 14 of recovery)

Female

Dose mg/kg	No.		Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	TP g/dL	Albumin g/dL	A/G
0	5	Mean	142	4.5	111	9.6	4.2	6.4	3.0	0.87
		S.D.	1	0.3	1	0.1	0.4	0.2	0.1	0.06
300	5	Mean	142	4.2	111	9.8	4.2	6.6*	3.1	0.86
		S.D.	2	0.3	1	0.2	0.6	0.1T	0.1	0.05

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

Table 8-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of male rats (Main group)

	Dose mg/kg		Body weight g	Brain g(g/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
		Mean	471	2.13	22.2	289	1.32	12.02
		S.D.	29	0.08	3.7	55	0.12	1.21
	12	No.	5	5	5	5	5	5
		Mean	472	2.07	20.2	294	1.34	12.39
		S.D.	19	0.11	3.3	47	0.06	1.16
	60	No.	12	5	5	5	5	5
		Mean	467	2.12	23.1	385	1.35	11.55
		S.D.	31	0.13	5.3	88	0.07	0.55
	300	No.	5	5	5	5	5	5
		Mean	452	2.03	21.7	266	1.37	11.99
		S.D.	22	0.03	1.6	46	0.15	1.61
Relative	0	No.		5	5	5	5	5
		Mean		0.45	4.7	61	0.28	2.55
		S.D.		0.03	0.6	9	0.02	0.16
	12	No.		5	5	5	5	5
		Mean		0.44	4.3	62	0.28	2.62
		S.D.		0.03	0.8	10	0.01	0.19
	60	No.		5	5	5	5	5
		Mean		0.45	4.9	82*	0.29	2.48
		S.D.		0.03	1.0	17D	0.02	0.10
	300	No.		5	5	5	5	5
		Mean		0.45	4.8	59	0.30	2.65
		S.D.		0.02	0.5	10	0.03	0.23

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

Table 8-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of male rats (Main group)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)	Body weight g	Testis (R+L) g(g/100g BW)	Epididymis (R+L) mg(mg/100g BW)
Absolute	0	No.	5	5	5	12	12	12
		Mean	0.80	3.20	66	465	3.16	1212
		S.D.	0.13	0.24	5	33	0.38	117
	12	No.	5	5	5	12	12	12
		Mean	0.74	3.16	66	468	3.23	1238
		S.D.	0.10	0.08	7	29	0.21	60
	60	No.	5	5	5	12	12	12
		Mean	0.79	3.33	69	467	3.20	1239
		S.D.	0.11	0.07	9	31	0.49	116
	300	No.	5	5	5	12	12	12
		Mean	0.70	3.28	59	450	3.34	1257
		S.D.	0.09	0.33	9	20	0.25	53
Relative	0	No.	5	5	5		12	12
		Mean	0.17	0.68	14		0.68	262
		S.D.	0.03	0.04	1		0.10	35
	12	No.	5	5	5		12	12
		Mean	0.16	0.67	14		0.69	266
		S.D.	0.02	0.04	2		0.06	21
	60	No.	5	5	5		12	12
		Mean	0.17	0.72	15		0.69	266
		S.D.	0.02	0.04	2		0.11	30
	300	No.	5	5	5		12	12
		Mean	0.15	0.72	13		0.74	280
		S.D.	0.01	0.04	2		0.07	13

No significant difference in any treated groups from control group.

Table 8-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of female rats (Main group)

	Dose mg/kg		Body weight g	Brain g(g/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
		Mean	295	1.97	16.1	232	0.95	9.95
		S.D.	7	0.03	2.3	88	0.03	0.21
	12	No.	5	5	5	5	5	5
		Mean	302	1.98	17.6	268	1.01	10.23
		S.D.	13	0.08	1.9	79	0.11	0.77
	60	No.	5	5	5	5	5	5
		Mean	298	1.91	18.6	234	1.01	10.31
		S.D.	10	0.11	2.3	44	0.10	0.68
	300	No.	5	5	5	5	5	5
		Mean	296	1.93	17.8	220	0.99	10.11
		S.D.	19	0.04	6.8	45	0.04	0.46
Relative	0	No.		5	5	5	5	5
		Mean		0.67	5.5	79	0.32	3.37
		S.D.		0.02	0.7	30	0.01	0.09
	12	No.		5	5	5	5	5
		Mean		0.66	5.8	89	0.33	3.39
		S.D.		0.04	0.5	25	0.03	0.21
	60	No.		5	5	5	5	5
		Mean		0.64	6.3	78	0.34	3.46
		S.D.		0.05	0.9	13	0.03	0.27
	300	No.		5	5	5	5	5
		Mean		0.66	6.1	74	0.33	3.42
		S.D.		0.04	2.5	16	0.02	0.16

No significant difference in any treated groups from control group.

Table 8-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of female rats (Main group)

	Dose mg/kg		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	No.	5	5	5
		Mean	0.58	1.98	94
		S.D.	0.05	0.15	11
	12	No.	5	5	5
		Mean	0.64	2.08	94
		S.D.	0.07	0.16	8
	60	No.	5	5	5
		Mean	0.68	2.01	99
		S.D.	0.10	0.26	20
	300	No.	5	5	5
		Mean	0.68	2.07	88
		S.D.	0.06	0.10	7
Relative	0	No.	5	5	5
		Mean	0.20	0.67	32
		S.D.	0.02	0.05	4
	12	No.	5	5	5
		Mean	0.21	0.69	31
		S.D.	0.02	0.05	3
	60	No.	5	5	5
		Mean	0.23	0.68	33
		S.D.	0.04	0.09	7
	300	No.	5	5	5
		Mean	0.23	0.70	30
		S.D.	0.01	0.04	3

No significant difference in any treated groups from control group.

Table 8-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of male rats (Recovery group)

	Dose mg/kg	No. of animals		Body weight g	Brain g(g/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	5	Mean	492	2.07	24.1	299	1.44	12.39
			S.D.	46	0.08	5.7	15	0.14	1.27
	300	5	Mean	477	2.12	24.1	270	1.41	13.47
			S.D.	30	0.12	4.4	58	0.05	1.46
Relative	0	5	Mean		0.42	4.9	61	0.30	2.52
			S.D.		0.03	0.9	3	0.04	0.07
	300	5	Mean		0.45	5.1	57	0.30	2.82*
			S.D.		0.02	1.0	14	0.02	0.24AT

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

Table 8-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of male rats (Recovery group)

	Dose mg/kg	No. of animals		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)
Absolute	0	5	Mean	0.69	3.20	57	3.18	1300
			S.D.	0.06	0.35	6	0.24	42
	300	5	Mean	0.88	3.54	56	3.51	1382
			S.D.	0.37	0.28	11	0.30	101
Relative	0	5	Mean	0.14	0.65	12	0.65	266
			S.D.	0.01	0.02	1	0.08	30
	300	5	Mean	0.19	0.74**	12	0.74	291
			S.D.	0.08	0.03T	2	0.04	28

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

Table 8-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of female rats (Recovery group)

	Dose mg/kg	No. of animals		Body weight g	Brain g(g/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	5	Mean	277	2.00	15.7	269	0.83	6.63
			S.D.	20	0.05	2.5	66	0.03	0.53
	300	5	Mean	276	1.96	16.8	311	0.91	7.28
			S.D.	16	0.03	2.7	93	0.08	0.46
Relative	0	5	Mean		0.73	5.7	97	0.30	2.40
			S.D.		0.04	0.9	22	0.02	0.11
	300	5	Mean		0.71	6.1	114	0.33	2.64**
			S.D.		0.03	0.9	35	0.04	0.11T

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

Table 8-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Organ weight of female rats (Recovery group)

	Dose mg/kg	No. of animals		Spleen g(g/100g BW)	Kidney (R+L) g(g/100g BW)	Adrenal (R+L) mg(mg/100g BW)
Absolute	0	5	Mean	0.52	1.73	72
			S.D.	0.09	0.12	12
	300	5	Mean	0.56	1.93	78
			S.D.	0.09	0.20	3
Relative	0	5	Mean	0.19	0.62	26
			S.D.	0.02	0.02	2
	300	5	Mean	0.20	0.70*	29
			S.D.	0.04	0.05T	2

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

Table 9-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Gross pathological findings (Main group)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	12	60	300	0	12	60	300
	Number:	12	12	12	12	12	12	12	12
Intestine,ileum									
Diverticulum		0	1	0	0	0	0	0	0
Intestine,cecum									
Dilatation		0	0	0	8	0	0	0	2
Kidney									
Focus,white		0	1	0	0	0	0	0	0
Pituitary									
Cyst		0	0	0	0	0	0	0	1
Stomach									
Nodule,serosal		0	0	1	0	0	0	0	1
Focus,dark red,glandular stomach		0	0	0	0	1	0	0	0
Thickening,limiting ridge		0	0	0	4	0	0	0	2
Urethra									
Nodule		0	0	0	0	0	1	0	0

Table 9-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Gross pathological findings (Recovery group)

Organs / Findings	Sex:	M	M	F	F
	Dose(mg/kg):	0	300	0	300
	Number:	5	5	5	5
Intestine,ileum					
Diverticulum		1	0	0	0
Kidney					
Cyst		1	0	0	0
Spleen					
Focus,raised		0	1	0	0

Table 10-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Histopathological findings (Main group)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	12	60	300	0	12	60	300
	Number:	12	12	12	12	12	12	12	12
Adrenal									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Bone+Bone marrow,femoral									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Bone+Bone marrow,sternal									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Cerebellum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Cerebrum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Epididymis									
Number examined		5	0	0	5	-	-	-	-
Not remarkable		4	0	0	5	-	-	-	-
Cell infiltration,interstitial		1	0	0	0	-	-	-	-
minimal		1	0	0	0	-	-	-	-
Heart									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		4	0	0	4	5	0	0	5
Myocarditis,focal		1	0	0	1	0	0	0	0
minimal		1	0	0	1	0	0	0	0
Intestine,duodenum									
Number examined		12	12	12	12	12	12	12	12
Not remarkable		12	12	12	6	12	12	12	7
Hypertrophy,mucosal epithelial		0	0	0	6	0	0	0	5
minimal		0	0	0	6	0	0	0	5
Intestine,jejunum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine,ileum									
Number examined		5	1	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Diverticulum		0	1	0	0	0	0	0	0
mild		0	1	0	0	0	0	0	0
Intestine,cecum									
Number examined		5	0	0	8	5	0	0	6
Not remarkable		4	0	0	5	4	0	0	6
Cell infiltration,mucosal		1	0	0	3	1	0	0	0
minimal		0	0	0	3	1	0	0	0
mild		1	0	0	0	0	0	0	0
Intestine,colon									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Intestine,rectum									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5

- : Not applicable

Table 10-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Histopathological findings (Main group)

Organs / Findings	Sex: / Dose(mg/kg): / Number:	M 0 12	M 12 12	M 60 12	M 300 12	F 0 12	F 12 12	F 60 12	F 300 12
Kidney									
Number examined		5	1	0	5	5	0	0	5
Not remarkable		2	1	0	4	5	0	0	4
Regeneration,tubular		3	0	0	1	0	0	0	0
minimal		3	0	0	1	0	0	0	0
Fibrosis,focal		0	0	0	0	0	0	0	1
minimal		0	0	0	0	0	0	0	1
Liver									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		1	0	0	2	4	0	0	3
Microgranuloma		4	0	0	3	1	0	0	2
minimal		4	0	0	3	1	0	0	2
Lung(bronchus)									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	4	0	0	4
Accumulation,foamy cell		0	0	0	0	1	0	0	1
minimal		0	0	0	0	1	0	0	1
Lymph node,mesenteric									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Lymph node,submandibular									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Parathyroid									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Pituitary									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	4
Cyst,anterior		0	0	0	0	0	0	0	1
mild		0	0	0	0	0	0	0	1
Sciatic nerve									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Seminal vesicle									
Number examined		5	0	0	5	-	-	-	-
Not remarkable		5	0	0	5	-	-	-	-
Spinal cord,thoracic									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Spleen									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		2	0	0	4	0	0	0	0
Hematopoiesis,extramedullary		3	0	0	1	5	0	0	5
minimal		3	0	0	1	5	0	0	5

- : Not applicable

Table 10-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Histopathological findings (Main group)

Organs / Findings	Sex:	M	M	M	M	F	F	F	F
	Dose(mg/kg):	0	12	60	300	0	12	60	300
	Number:	12	12	12	12	12	12	12	12
Stomach									
Number examined		5	0	1	7	5	0	0	7
Not remarkable		5	0	0	7	4	0	0	6
Cyst,epidermal		0	0	1	0	0	0	0	1
minimal		0	0	0	0	0	0	0	1
mild		0	0	1	0	0	0	0	0
Erosion,glandular stomach		0	0	0	0	1	0	0	0
minimal		0	0	0	0	1	0	0	0
Testis									
Number examined		5	0	0	5	-	-	-	-
Not remarkable		5	0	0	4	-	-	-	-
Atrophy,seminiferous tubular		0	0	0	1	-	-	-	-
minimal		0	0	0	1	-	-	-	-
Thyroid									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		4	0	0	5	4	0	0	5
Cyst,ultimobranchial		1	0	0	0	1	0	0	0
minimal		1	0	0	0	1	0	0	0
Thymus									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	5	0	0	5
Urinary bladder									
Number examined		5	0	0	5	5	0	0	5
Not remarkable		5	0	0	5	4	0	0	5
Cell infiltration,subcutaneous		0	0	0	0	1	0	0	0
minimal		0	0	0	0	1	0	0	0
Uterus									
Number examined		-	-	-	-	5	0	0	5
Not remarkable		-	-	-	-	5	0	0	5
Urethra									
Number examined		0	0	0	0	0	1	0	0
Calculus		0	0	0	0	0	1	0	0
mild		0	0	0	0	0	1	0	0

- : Not applicable

Table 10-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Histopathological findings (Recovery group)

Organs	Sex:	M	M	F	F
	Dose(mg/kg):	0	300	0	300
Findings	Number:	5	5	5	5
Intestine,duodenum					
Number examined		5	5	5	5
Not remarkable		5	5	5	5
Intestine,ileum					
Number examined		1	0	0	0
Diverticulum		1	0	0	0
mild		1	0	0	0
Kidney					
Number examined		1	0	0	0
Dilatation,tubular,cystic		1	0	0	0
mild		1	0	0	0
Spleen					
Number examined		0	1	0	0
Granuloma		0	1	0	0
mild		0	1	0	0

Table 11 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

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.
		0	1	2	3	4	Mean±S.D.	
0	12	0	0	0	6	6	3.5±0.5	4.0±0.1
12	12	0	0	0	9	3	3.3±0.5	4.0±0.1
60	12	0	0	0	5	7	3.6±0.5	4.1±0.3
300	12	0	0	0	6	6	3.5±0.5	4.2±0.4

No significant difference in any treated groups from control group.

Table 12 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

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	2.8±1.0	12/12(100.0)	12/12(100.0)	12	2.8±1.0	12/12(100.0)	12/12(100.0)
12	12	2.7±2.5	12/12(100.0)	11/12(91.7)	12	2.7±2.5	12/12(100.0)	11/12(91.7)
60	12	2.7±1.2	12/12(100.0)	12/12(100.0)	12	2.7±1.2	12/12(100.0)	12/12(100.0)
300	12	2.4±1.2	12/12(100.0)	10/12(83.3)	12	2.4±1.2	12/12(100.0)	10/12(83.3)

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

Table 13 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Delivery data on dams

Dose mg/kg		No. of pregnant females	No. of females with live pups	Delivery index % a)	Gestation period	No. of corpora lutea	No. of implantation sites	Implantation index % b)	No. of stillborn pups (%)c)	No. of liveborn pups	Live birth index % d)
0	Total	12	12	100.0		183	173		2	163	
	Mean				21.9	15.3	14.4	93.3	(1.3)	13.6	98.7
	S.D.				0.5	2.7	3.6	14.2	(4.4)	3.3	4.4
12	Total	11	11	100.0		172	169		3	163	
	Mean				22.0	15.6	15.4	98.2	(1.9)	14.8	98.1
	S.D.				0.5	1.4	1.4	3.0	(4.4)	1.8	4.4
60	Total	12	12	100.0		188	181		2	171	
	Mean				22.1	15.7	15.1	96.4	(1.3)	14.3	98.7
	S.D.				0.5	1.5	1.5	4.8	(3.0)	1.8	3.0
300	Total	10	10	100.0		151	148		2	135	
	Mean				22.2	15.1	14.8	98.3	(1.4)	13.5	98.6
	S.D.				0.2	1.6	1.1	3.8	(3.0)	1.1	3.0

a): (No. of females which delivered live pups / No. of pregnant females) × 100
b): (No. of implantation sites / No. of corpora lutea) × 100
c): (No. of stillborn pups / No. of stillborn and liveborn pups) × 100
d): (No. of liveborn pups / No. of stillborn and liveborn pups) × 100
No significant difference in any treated groups from control group.

Table 14 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

External examination of liveborn pups

Dose mg/kg	No. of dams		No. of males	No. of females	Sex ratio a)	Body weight(g) Male	Body weight(g) Female	External abnormalities(%)c) b)
		Total	90	73	0.55			0
0	12	Mean	7.5	6.1		6.5	6.2	(0.0)
		S.D.	2.9	2.2		0.6	0.5	(0.0)
		Total	87	76	0.53			0
12	11	Mean	7.9	6.9		6.4	6.0	(0.0)
		S.D.	2.1	2.0		0.4	0.5	(0.0)
		Total	88	83	0.51			0
60	12	Mean	7.3	6.9		6.5	6.2	(0.0)
		S.D.	1.7	2.3		0.4	0.3	(0.0)
		Total	65	70	0.48			1d)
300	10	Mean	6.5	7.0		6.9	6.5	(0.7)
		S.D.	1.6	1.2		0.4	0.3	(2.2)

a): No. of males / No. of liveborn pups
b): No. of liveborn pups with external abnormalities
c): (No. of liveborn pups with external abnormalities / No. of liveborn pups) × 100
d): Vestigial tail
No significant difference in any treated groups from control group.

Table 15 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Viability index of pups

Dose mg/kg		No. of dams	No. of live pups		Viability index on day 4 after birth % a)
			Day 0	Day 4	
0	Total	12	163	162	
	Mean		13.6	13.5	99.5
	S.D.		3.3	3.3	1.8
12	Total	11	163	159	
	Mean		14.8	14.5	97.8
	S.D.		1.8	1.4	3.9
60	Total	12	171	169	
	Mean		14.3	14.1	99.0
	S.D.		1.8	1.6	2.4
300	Total	10	135	133	
	Mean		13.5	13.3	98.6
	S.D.		1.1	1.2	4.5

a): (No. of live pups on day 4 / No. of liveborn pups on day 0) × 100
No significant difference in any treated groups from control group.

Table 16 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Body weight of pups

Dose mg/kg		Male		Female	
		0	4	0	4a)
0	No.	12	12	12	12
	Mean	6.5	10.1	6.2	9.7
	S.D.	0.6	1.5	0.5	1.5
12	No.	11	11	11	11
	Mean	6.4	9.7	6.0	9.1
	S.D.	0.4	1.0	0.5	1.0
60	No.	12	12	12	12
	Mean	6.5	9.8	6.2	9.4
	S.D.	0.4	0.7	0.3	0.5
300	No.	10	10	10	10
	Mean	6.9	10.3	6.5	9.7
	S.D.	0.4	1.1	0.3	1.0

Unit: g
No.: No. of dams
a): Day after birth
No significant difference in any treated groups from control group.

Table 17 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with Benzenesulfonic acid,4-hydroxy-,tin(2+)salt

Gross pathological findings in pups on day 4 after birth

Dose (mg/kg)	0	12	60	300
Male				
No. of pups examined	89	86	87	64
No. of pups with abnormal findings	0	0	0	0
Female				
No. of pups examined	73	73	82	67a)
No. of pups with abnormal findings	0	0	0	0

a): Loss of two pups during the lactation period.