



食薬セ研第10-1627号

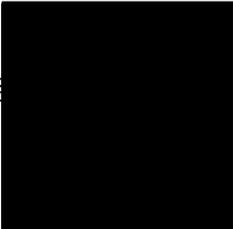
2000年 8月25日

N,N,N-トリメチルメタンアミン
ヒドロキシドの
ラットを用いる28日間反復経口投与毒性試験
(回復14日間)

厚生省生活衛生局 委託

財団法人食品薬品

秦野研



試験委託者 : 厚生省生活衛生局

試験計画番号 : C-98-005

被験物質名 : N,N,N-トリメチルメタンアミンヒドロキシド (CAS No. : 75-59-2)

試験項目 : 反復投与毒性試験

試験内容 : ラットを用いる28日間反復経口投与毒性試験 (回復14日間)

試験開始日 : 1999年 2月 4日

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資料保管場所 : 秦野研究所資料保管室

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試験施設 : 財団法人食品薬品安全センター秦野研究所
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所長

0年 8月25日

信頼性保証証明書

試験の表題 : *N,N,N*-トリメチルメタンアミンヒドロキシドのラットを用いる
28日間反復経口投与毒性試験 (回復14日間)

試験計画番号 : C-98-005

本試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	1999年 2月 4日	1999年 2月 4日
試験計画書修正書		
C-98-005~修①	1999年 2月23日	1999年 2月23日
C-98-005~修②	2000年 4月10日	2000年 4月10日
動物の受入れおよび検疫	1999年 2月17日	1999年 2月17日
検体調製および含量試験	1999年 2月25日	1999年 2月25日
投与	1999年 2月25日	1999年 2月25日
体重測定	1999年 3月 1日	1999年 3月 1日
尿検査	1999年 3月23日	1999年 3月23日
剖検・器官重量測定・血液学 検査および生化学検査	1999年 3月25日	1999年 3月25日
病理学検査	1999年 5月19日	1999年 5月24日
報告書案 (第一次)	1999年 7月19日	1999年 7月19日
報告書案 (第二次)	2000年 7月19日	2000年 7月19日
最終報告書	2000年 8月25日	2000年 8月25日

本試験は、「新規化学物質に係る試験及び指定化学物質に係る有害性の調査の項目等を定める命令第4条に規定する試験施設について (化学物質GLP)」 (昭和59年3月31日、環保業第39号、薬発第229号、59基局第85号、改正昭和63年11月18日、環企研第233号、衛生第38号、63基局第823号) に準拠して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを証明する。

2000年 8月25日

財団法人食品薬品安全センター

秦野研究所 信頼性保証責任者



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【要 約】

N,N,N-トリメチルメタンアミンヒドロキシドの28日間反復経口投与毒性試験（回復14日間）を雌雄の Sprague-Dawley 系ラットを用いて実施した。雌雄とも4群構成とし、1群には媒体である注射用水を、他の3群には被験物質を、それぞれ5、10 および 20 mg/kg の用量で28日間にわたり強制経口投与した。雌雄とも回復試験に用いる動物を含む対照群および 20 mg/kg 投与群は各10匹、その他の群は各5匹とした。今回の試験において認められた主な変化を以下に要約する。

一般状態の変化として、投与第6日以降、10 mg/kg 以上の投与群で投与直後の流涎が繰り返して観察された。この流涎は、投与後1時間以内に消失する一過性の症状であったが、投与第13日以降には、雄の 10 mg/kg 以上の投与群および雌の 20 mg/kg 投与群では、投与後1時間以上継続して観察される例があった。

10 mg/kg 投与群の雄および 20 mg/kg 投与群の雌雄では、投与第1週の摂餌量が有意な低値を示した。また、回復試験期間中に被験物質投与群の雄の摂餌量は高値を示し、回復第1週には有意な差が認められた。この他には、体重および摂餌量のいずれにも有意な差は認められなかった。

回復第2週の尿検査で、被験物質投与群の雄における電解質排泄量に有意な増加がみられたが、投与第4週の尿検査所見には、被験物質投与に起因したと考えられる変化はなかった。

血液学検査所見として、投与期間終了時には、いずれの検査項目にも被験物質投与に起因した変化は認められなかった。また、回復試験期間終了時では、被験物質投与群の雌雄に赤血球数の有意な減少等がみられたが、いずれも生理的変動範囲内の軽微な変化であった。生化学検査所見には、被験物質投与に起因したと考えられる変化は認められなかった。

器官重量では、投与期間終了時の雄の心臓重量が用量に依存して減少した。すなわち、絶対重量は 5 mg/kg 以上の投与群で、相対重量は 10 mg/kg 以上の投与群で、いずれも有意な減少が認められた。一方、投与期間終了時の雌および回復試験期間終了時の雌雄の器官重量には、いずれも有意な差は認められなかった。また、組織学所見には、被験物質投与に起因したと考えられる変化は観察されなかった。

以上のように、*N,N,N*-トリメチルメタンアミンヒドロキシドを反復投与することにより、10 mg/kg 以上の用量では、投与後の流涎がみられ、20 mg/kg の用量では、流涎が1時間以上継続して認められる例が多かった。また、雄では心臓の重量が用量依存的に減少し、5 mg/kg 以上の用量で絶対重量に有意な差が認められた。したがって、本試験条件下における *N,N,N*-トリメチルメタンアミンヒドロキシドの無影響量は、雄では 5 mg/kg 未満、雌では 5 mg/kg であると考えられる。

【緒 言】

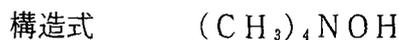
N,N,N-トリメチルメタンアミンヒドロキシドのラットにおける単回経口投与時のLD₅₀は50 mg/kgであることが報告されている（被験物質提供元資料）。今回、OECD 既存化学物質安全性点検等に係る毒性調査の一環として、*N,N,N*-トリメチルメタンアミンヒドロキシドの安全性確認の資料を得るために、ラットにおける28日間反復経口投与毒性試験および14日間回復試験を実施した。

なお、本試験は、「化審法毒性試験法、スクリーニング毒性試験－ほ乳類を用いる28日間の反復投与毒性試験－」（昭和61年12月5日、環保業第700号、薬発第1039号、61基局第1014号）および「化学物質GLP」（昭和59年3月31日、環保業第39号、薬発第229号、59基局第85号、昭和63年11月18日改正、環企研第233号、衛生第38号、63基局第823号）に準拠して実施した。

【方 法】

1. 被験物質

被験物質として、*N,N,N*-トリメチルメタンアミンヒドロキシド（以下 TMAH と略記）を用いた。本被験物質は、別名を水酸化テトラメチルアンモニウムと称し、英名は *N,N,N*-trimethylmethanaminium hydroxide であり、CAS No. 75-59-2、分子量 91.03、分子式 $C_4H_{13}NO$ である。TMAH の構造式を以下に示す。



本試験には、XXXXXXXXXXより提供された TMAH の 20.19 wt%水溶液（ロット番号：XXXXXXXXXX）を用いた。提供された水溶液は無色透明の液体で、不純物として炭酸根 3 ppm、塩化物 0.17 ppm を含有していた。受領物質は、使用時まで被験物質受領保管室において、室温で保管した。

2. 使用動物および飼育方法

生後4週で購入した雌雄の Sprague-Dawley 系ラット [Crj:CD(SD)IGS、SPF、日本チャールス・リバー株式会社、筑波飼育センター] (注1) を検疫と馴化を兼ねて8日間にわたり予備飼育した後、一般状態に異常の認められなかった雌雄各30匹を試験に供した(注2)。動物は、全飼育期間を通じて、基準温度 $24 \pm 1^\circ C$ 、基準湿度 50~65%、換気回数約15回/時、照明12時間(7~19時点灯)に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に1匹ずつ収容し、固型飼料(CE-2、日本クレア株式会社)および水道水(秦野市水道局給水)を自由摂取させて飼育した。なお、飼育期間中、飼育室の温度の実測値は、基準値の範囲内にあり、湿度の実測値は、空調機の管理作業あるいは日常的湿式清掃による1時間以内の逸脱を除いて基準値内にあった(注3)。また、供給し

(注1)

動物購入日: 1999年2月17日
入荷匹数: 雄34匹 雌34匹
入荷時体重: 雄78.1~87.8g (平均82.9g) 雌75.1~82.5g (平均78.3g)

(注2)

投与開始日: 1999年2月25日
投与開始時体重: 雄158.2~174.6g (平均165.9g) 雌132.2~151.1g (平均141.2g)

(注3)

動物飼育期間中の温湿度の実測値 温度23~25℃ 湿度47~69%

た飼料および水には、試験に支障を来す可能性のある混入物はなかった。

各動物の耳介には、耳パンチを用いて一連の動物番号を標識し、また、群ごとに色の異なる動物カードに試験計画番号、性別、群（投与量）、動物番号を記入して飼育ケージに掛け、個体識別の補助とした。

3. 投与検体の調製

投与検体は、供給物質を局方注射用水（製造番号：9707SA、光製薬株式会社）で希釈して被験物質濃度として 0.2 w/v% 溶液を調製し、これを注射用水により各濃度に段階希釈した。

なお、秦野研究所にて、初回に調製した各濃度の投与検体の含量測定を実施した結果、溶液中の被験物質の平均含量は、所定濃度の 100~101%であった（Appendix A）。また、本被験物質の溶媒中の安定性を確認するための分析法の確立が困難であったため、安定性試験は実施せず、投与検体は用時調製とした。なお、本投与検体は溶液であることから、均一性試験は実施しなかった。調製検体中の被験物質の濃度は、滴定法により測定した（Appendix B）。

4. 群および群分け

本試験の投与量は、投与量設定のための予備試験〔試験計画番号：C-98-004、投与量：0、1、5 および 10 mg/kg（7日間投与）、20 mg/kg（5日間投与）〕と急性経口投与毒性予備試験（試験計画番号：A-98-026）の結果に基づき決定した。すなわち、TMAH を7日間（20 mg/kg 投与群は5日間）反復投与することにより 20 mg/kg 投与群の雄1例で、腺胃粘膜の肥厚が観察されたが、10 mg/kg 以下の投与群では何ら変化がみられなかった。一方、TMAH の急性経口投与毒性予備試験の 25 mg/kg 投与群で、半眼および自発運動の減少等が散見され、雄1例では投与翌日の体重が減少した。これらのことから 20 mg/kg 投与群は、被験物質による毒性影響が認められ、かつ28日間の反復投与に耐えうる用量であると判断し、本試験の用量は、高用量を 20 mg/kg とし、以下公比2で除して 10 および 5 mg/kg を中用量および低用量とした。また、雌雄とも媒体である注射用水を投与する対照群を設けた。なお、雌雄とも回復試験を行う対照群および 20 mg/kg 投与群は各10匹、その他の群は各5匹とした。

群分けは、検疫終了時の測定体重をもとに体重別層化無作為抽出法により行った。各群

の投与量および動物番号等を以下に示した。

群	投与量 (mg/kg)	投与容量 (mL/kg)	動物番号	
			雄	雌
対 照 群	0	10	1～10	31～40
低用量群	5	10	11～15	41～45
中用量群	10	10	16～20	46～50
高用量群	20	10	21～30	51～60

雌雄とも対照群および 20 mg/kg 投与群では、動物番号の若い方から 5 匹を回復試験に用いた。

5. 投与方法

投与経路は、化審法ガイドラインに従い経口とした。投与時刻は12時から15時の間とし、1日1回、28日間、ラット用胃管を用いて投与した。投与容量は 10 mL/kg とし、各投与時の最近時の体重をもとに個体別に算出した。

なお、投与期間中の日数および週の表記法は、投与開始日および投与開始週をそれぞれ投与第1日および投与第1週とし、回復試験期間中の日数および週の表記法もこれに準じて回復第1日および回復第1週とした。

6. 検査項目

1) 一般検査

全例について、毎日（投与期間中は投与前および投与後）一般状態の観察を行った。また、全例の体重および摂餌量を以下のとおり測定した。体重は、投与第1週には投与第1日の投与直前と投与第5日、投与第2週以降の投与期間および回復試験期間中は1週に2回の頻度で測定した。その他、投与期間終了日、回復試験期間終了日および剖検日にも測定した。摂餌量は、投与第1週では、投与第1日から2日にかけて1日あたりの摂餌量を測定し、以後回復試験期間終了週まで毎週1回の頻度で測定した。

2) 尿検査

各群とも生存している全例について、投与第4週および回復試験期間終了週に動物を代謝ケージに收容し、以下の項目について検査した。ただし試験紙による検査および色調・混濁度は4時間あるいは新鮮尿で、その他の項目は約24時間の蓄尿で検査した。なお、尿

中電解質については、各濃度に尿量を乗じて1日あたりの排泄量を算出したほか、ナトリウム/カリウム比を算出した。

項 目	測 定 法	使 用 機 器
尿量	計 量	天秤
比重	重量法	天秤
色調・混濁度	視 診	—
pH・潜血・蛋白・糖・ケトン体	試験紙法	クリニテック 200+ (バイエル・三共)
カリウム濃度	同上	同上
ナトリウム濃度	イオン電極法	全自動電解質分析装置 EA05 (A&T)
カルシウム濃度	同上	同上
塩素濃度	同上	同上

3) 血液学検査

投与期間終了時および回復試験期間終了時に解剖を行った動物（以下、定期解剖例と記す）は、全例採血前（屠殺剖検前）に18～24時間絶食させた。その後、ペントバルビタールナトリウム麻酔下で、腹部後大静脈から抗凝固剤として EDTA-2K を用いて採血し、以下の項目について検査した。なお、プロトロンビン時間および活性部分トロンボプラスチン時間の測定に用いる血液については、クエン酸ナトリウムを抗凝固剤として用いて採取した。

項 目	測 定 法	使 用 機 器
赤血球数 (RBC)	自動 (電気抵抗法)	Coulter Counter Model S-PLUS IV (コルター-エレクトロニクス)
白血球数 (WBC)	同上 (同上)	同上
血色素量 (Hb)	同上 (吸光度法)	同上
平均赤血球容積 (MCV)	同上 (電気抵抗法)	同上
血小板数	同上 (同上)	同上
ヘマトクリット値 (Ht)	計算 (RBC×MCV×0.001)	
平均赤血球血色素量 (MCH)	同上 (Hb×1000/RBC)	
平均赤血球血色素濃度 (MCHC)	同上 (Hb×100/Ht)	
白血球分類	視算 (静脈血塗抹標本 Wright-Giemsa 染色)	光学顕微鏡
網状赤血球比率	Brecher 法	同上
プロトロンビン時間 (PT)	光散乱検出法	CA-1000 (東亜医用電子)
活性部分トロンボプラスチン時間 (APTT)	同上	同上

4) 生化学検査

前述の採血に引き続き、同様の麻酔および採血部位の条件下で、全例からヘパリンを抗凝固剤として採取した血液について、以下の項目を検査した。

項 目	測 定 法	使 用 機 器
総蛋白濃度	ビレット法	遠心方式生化学自動分析装置 COBAS-FARA (ロシ)
アルミン濃度	BCG法	同上
総コレステロール濃度	COD-DAOS法	同上
ブドウ糖濃度	グルコキナーゼ G6PDH法	同上
尿素窒素濃度 (BUN)	ウレアゼ G ₀ . DH法	同上
クレアチン濃度	Jaffe法 (Rate)	同上
ALP活性	GSCC法	同上
GOT活性	IFCC法	同上
GPT活性	同上	同上
γ-GTP活性	γ-グルタミル-3-カルボキシ-4-ニトロアニリド基質法	同上
トリグリセリド濃度	GPO・DAOS法	同上
無機リン濃度 (Inorg. phos.)	モリブデン酸直接法	同上
カルシウム濃度	OCPC法	同上
A/G比	計算	
ナトリウム濃度	イオン電極法	全自動電解質分析装置 EA05 (A&T)
カリウム濃度	同上	同上
塩素濃度	同上	同上

5) 病理学検査

採血後、必要に応じて腋窩動脈を切断して放血屠殺した後、器官および組織を肉眼的に観察し、各動物の以下に示す器官の重量を測定した。また、各器官重量を剖検日の体重で除してそれぞれの相対重量を算出した。

重 量 測 定 器 官

脳、心臓、肝臓、腎臓、胸腺、脾臓、副腎、精巣、精巣上体、卵巣

肉眼的観察に引き続き、以下の器官あるいは組織を摘出して保存した。なお、精巣および精巣上体はブアン液に固定し（長期保存は 0.1 M リン酸緩衝10%ホルマリン溶液を使用した）、その他の器官・組織は 0.1 M リン酸緩衝10%ホルマリン溶液に固定した。さらに、投与期間終了時の全群の*印を付した器官・組織をパラフィン包埋して薄切し、ヘマトキシリン・エオジン染色標本を作製した。その後、光学顕微鏡を用いて、対照群および高用量群の組織学的検査を実施した。

その結果、投与期間終了時の対照群と高用量群の組織学検査で、雄の腎臓に被験物質投与との関連が疑われる変化が認められたため、他の群でも組織学検査を実施した。

固 定 ・ 保 存 器 官 ・ 組 織

脳、下垂体、脊髄、眼球、甲状腺、上皮小体、心臓*、気管、気管支、肺、肝臓*、腎臓*、胸腺、脾臓*、副腎*、胃*、十二指腸、空腸、回腸、盲腸、結腸、直腸、精巣*、精巣上体*、前立腺、精嚢、卵巣*、子宮、腔、乳腺、膀胱、下顎リンパ節、腸間膜リンパ節、骨格筋（下腿部）、坐骨神経、大腿骨骨髓、膵臓、顎下腺、舌下腺、舌、食道、大動脈、ハーダー腺、皮膚、病変部

7. データ解析法

体重、摂餌量、半定量検査を除く尿検査ならびに定期解剖例の血液学検査、生化学検査の値および器官重量は、群ごとに平均値および標準偏差を求めた。また、試験群の構成が対照群を含めて3群以上あった場合は、Bartlettの方法により分散の一意性について検定（有意水準：5%）を行った。分散が一意である場合には一元配置型の分散分析を行い、群間に有意性（有意水準：5%）が認められた場合は、Dunnett法により多重比較を行った。また、分散が一意でない場合は、Kruskal-Wallisの順位検定を行い、群間に有意性（有意水準：5%）が認められた場合には、Dunnett型の検定法で多重比較を行った。但し、いずれかの群で分散が0となった場合には、Bartlett法による検定は行わずにKruskal-Wallisの順位検定を行い、その結果、群間に有意性が認められた場合には、Dunnett型の検定法により多重比較を行った。一方、試験群が対照群を含め2群となった場合には、対照群と被験物質投与群の各平均値の差の検定は、各群の平均値および標準偏差値を求めた後、F-検定（有意水準：5%）を行い、等分散の場合にはStudentのt検定法、不等分散の場合にはAspin-Welchのt検定法を用いて有意差検定を行った。但し、どちらかの群で分散が0となった場合には、t検定は実施しなかった。さらに、病理組織所見中グレード分けしたデータはMann-WhitneyのU検定（両側検定）法により、また、陽性グレードの合計値はFisherの直接確率片側検定法により、対照群と被験物質投与群との間の有意差検定を行った（有意水準：5%）。

【結 果】

1. 死亡例

投与期間および回復試験期間中に死亡例はなかった。

2. 一般状態 (Table 1、Appendix 1)

投与第6日以降、投与後1時間以内に消失する投与直後の一過性の流涎が、5 mg/kg 投与群の雄1例、10 mg/kg 投与群の雄4例、雌5例、20 mg/kg 投与群の雄8例、雌9例に認められた。また、投与第13日以降には、流涎が投与後1時間以上継続して観察される例もあり、その例数は、10 mg/kg 投与群の雄1例、20 mg/kg 投与群の雄5例、雌6例であった。これらの流涎は、5 mg/kg 投与群を除き、投与により繰り返して観察されることが多かった。また、個体によっては投与時の保定の段階でみられることがあった。さらに、20 mg/kg 投与群の雌1例では、投与1時間後から流涎が認められることもあった。その他、10 mg/kg 投与群の雄1例では、投与第12日以降、片側眼球の暗色化が認められた。

3. 体重 (Fig. 1、Table 2、Appendix 2)

観察期間中、被験物質投与群では、雌雄いずれにおいても対照群との間に体重の有意な差は認められなかった。

4. 摂餌量 (Fig. 2、Table 3、Appendix 3)

10 mg/kg 投与群の雄および 20 mg/kg 投与群の雌雄では、投与第1週の摂餌量が対照群と比較して有意な低値を示したが、その後の投与期間中には、いずれの被験物質投与群においても有意な差は認められなかった。一方、回復試験期間中、被験物質投与群の雄の摂餌量は高値を示し、回復第1週には有意な差が認められた。

5. 尿検査所見 (Table 4、Appendix 4)

投与第4週の検査では、いずれの検査項目においても、対照群と被験物質投与群の間に著しい差は認められなかった。回復第2週の検査では、被験物質投与群の雄における電解質排泄量に有意な増加が認められた。

6. 血液学検査所見 (Table 5、Appendix 5)

投与期間終了時の検査では、20 mg/kg 投与群の雄にプロトロンビン時間の短縮がみられた以外、対照群と被験物質投与群の間に有意な差は認められなかった。また、回復試験期間終了時の検査では、被験物質投与群の雌雄に赤血球数の有意な減少がみられたほか、雄では網状赤血球比率、平均赤血球容積および平均赤血球血色素量の増加と血小板数の減少が、また、雌では血色素量の減少および活性部分トロンボプラスチン時間の短縮が認められた。

7. 生化学検査所見 (Table 6、Appendix 6)

投与期間終了時の検査では、いずれの検査項目においても、対照群と被験物質投与群の間に有意な差は認められなかった。回復試験期間終了時の雄では、総蛋白濃度の有意な低下が認められたが、他の検査項目には対照群と被験物質投与群の間に有意な差は認められなかった。

8. 病理学検査所見

1) 器官重量 (Table 7, 8、Appendix 7, 8)

投与期間終了時解剖例の 5 mg/kg 以上の投与群の雄では、心臓の絶対重量に有意な減少がみられ、10 mg/kg 以上の投与群では、相対重量にも有意な減少が認められた。一方、回復試験期間終了時解剖例の器官重量には、いずれも有意な差は認められなかった。

2) 肉眼所見 (Table 9、Appendix 9)

(1)投与期間終了時解剖例

片側眼球の暗色部が 10 mg/kg 投与群の雄 1 例に、腎臓の嚢胞が対照群の雌 1 例に、脾臓の小型化が 20 mg/kg 投与群の雌 1 例に観察された。

(2)回復試験期間終了時解剖例

腎臓の大型化と皮質の淡色部が 20 mg/kg 投与群の雄 1 例に、片側の精巣および精巣上体の小型化が対照群の 1 例に観察された。

3) 組織学検査所見 (Table 10、Appendix 10)

(1) 投与期間終了時解剖例

腎臓の近位尿細管に軽度な好酸性小体 (Photo) が 20 mg/kg 投与群の雄 2 例に観察されたほか、腎臓、脾臓あるいは心臓に Table 10-1-1 および 10-1-2 に示す所見が観察されたが、いずれの所見も群間でその発生頻度および程度に差は認められなかった。なお、肉眼的に病変がみられた部位の所見として、片側眼球に暗色部がみられた 10 mg/kg 投与群の雄 1 例では硝子体の出血が、腎臓に嚢胞がみられた対照群の雌 1 例では皮質の嚢胞が、脾臓の小型化がみられた 20 mg/kg 投与群の雌 1 例では、髄外造血の消失がそれぞれ認められた。

(2) 回復試験期間終了時解剖例

雄の腎臓の近位尿細管に軽微から軽度な好酸性小体が、対照群 2 例、被験物質投与群 3 例に観察されたほか、Table 10-2-1 に示す所見が観察されたが、いずれの所見も群間でその発生頻度および程度に差は認められなかった。なお、肉眼的に病変がみられた部位の所見として、片側の精巣および精巣上体の小型化がみられた対照群の 1 例では、精巣の精細管萎縮および精巣上体の精子減少が観察されたが、腎臓の大型化と皮質の淡色部がみられた 20 mg/kg 投与群の雄 1 例では、これに対応すると考えられる変化は認められなかった。

【考 察】

TMAH を、5、10 および 20 mg/kg の用量で雌雄の Sprague-Dawley 系ラットに 28日間にわたって強制経口投与し、その後14日間の回復試験期間を設けた。

その結果、投与第6日以降、被験物質投与群に投与直後の流涎が認められた。この流涎は、投与後1時間以内に消失する一過性の症状であったが、投与第13日以降には、雄の 10 mg/kg 以上の投与群および雌の 20 mg/kg 投与群では、投与後1時間以上継続して観察される例があった。流涎は、TMAH の急性経口投与毒性試験の高用量群 (50 mg/kg) でも観察されており、被験物質投与による影響と考えられる。流涎の成因としては、TMAH の 0.2 w/v% 水溶液の pH は 12.5 という強アルカリ性であることから、投与検体の刺激性による変化とも考えられるが、低用量の投与検体濃度でも pH はほとんど変わらないことから、その可能性は少ないと考えられる。一方、テトラメチルアンモニウム塩は神経節興奮薬 (脱分極性薬物) であり、一部ムスカリン様作用を有する¹⁾ ことから、被験物質の自律神経系に対する作用によって、唾液の分泌が亢進した可能性がある。なお、流涎以外に、便の性状あるいは瞳孔等には変化は認められなかった。また、5 mg/kg 投与群の雄1例に認められた流涎は、1回のみで、投与の保定の段階でみられていることから、被験物質の作用による症状ではなく、投与操作に反応した変化と考えられる。

10 mg/kg 投与群の雄および 20 mg/kg 投与群の雌雄では、投与第1週の摂餌量が低値を示した。この変化は、用量依存的事から被験物質投与によるものと考えられるが、観察期間中の体重には変化はなく、その影響は軽微なものであった。一方、回復試験期間中の被験物質投与群の雄の摂餌量が高値を示した。その成因については不明であるが、被験物質投与中止による変化と考えられる。また、回復第2週の尿検査で、被験物質投与群の雄の電解質排泄量に増加がみられたが、この所見は、前述の回復試験期間になつてからの摂餌量の増加に伴う変化の可能性がある。

回復試験期間終了時の血液学検査所見として、被験物質投与群の雌雄に赤血球数の減少がみられたほか、雄では網状赤血球比率、平均赤血球容積および平均赤血球血色素量の増加と血小板数の減少が、雌では血色素量の減少がそれぞれ認められた。これらの変化は、いずれも投与期間終了時には対照群との差はなく、また、生理的変動範囲内の軽微な変化であることから、毒性学的意義は少ないものと考えられる。この他、血液、生化学の検査

項目で、対照群と被験物質投与群との間に有意差の認められた血液凝固時間は、いずれも延長ではなく、短縮方向の変化であったこと、総蛋白濃度の低下は、投与期間終了時には変化はなく、他の関連所見もなかったことから、いずれも被験物質投与およびその後続く回復試験期間に関連がない変化と考えられる。

器官重量では、投与期間終了時に雄の心臓重量が用量に依存して減少したが、高用量群における組織学所見には対照群との差はなかった。前述のように、テトラメチルアンモニウム塩は神経節興奮薬であり、神経節のシナプス後膜の脱分極を生じて、節後ニューロンの興奮を起こし、次いで脱分極性の遮断を起こすことが知られており¹⁾、また、ラットの心臓に対してムスカリン様作用を有することが報告されている²⁾。これらのことから、今回の試験でみられた雄の心臓重量の減少は、被験物質投与による降圧、心筋の収縮力低下、心拍数の減少等心臓に対する負荷の軽減によって生じた可能性があるが、その詳細については不明である。

その他、病理学検査所見として、投与期間終了時に、20 mg/kg 投与群の雄 2 例で腎臓の近位尿細管に好酸性小体が観察されたが、この所見は、雄ラットに特徴的な自然発症性病変であり³⁾、回復試験期間終了時の検査では、対照群でも認められていることから、投与期間終了時に観察された変化は、自然発症性のもので、被験物質投与に起因した変化ではないと考えられる。

以上のように、TMAH を反復投与することにより、10 mg/kg 以上の用量では、投与後の流涎がみられ、20 mg/kg の用量では、流涎が1時間以上継続して認められる例が多かった。また、雄では心臓の重量が用量依存的に減少し、5 mg/kg 以上の用量で絶対重量に有意な差が認められた。したがって、本試験条件下における TMAH の無影響量は、雄では 5 mg/kg 未満、雌では 5 mg/kg であると考えられる。

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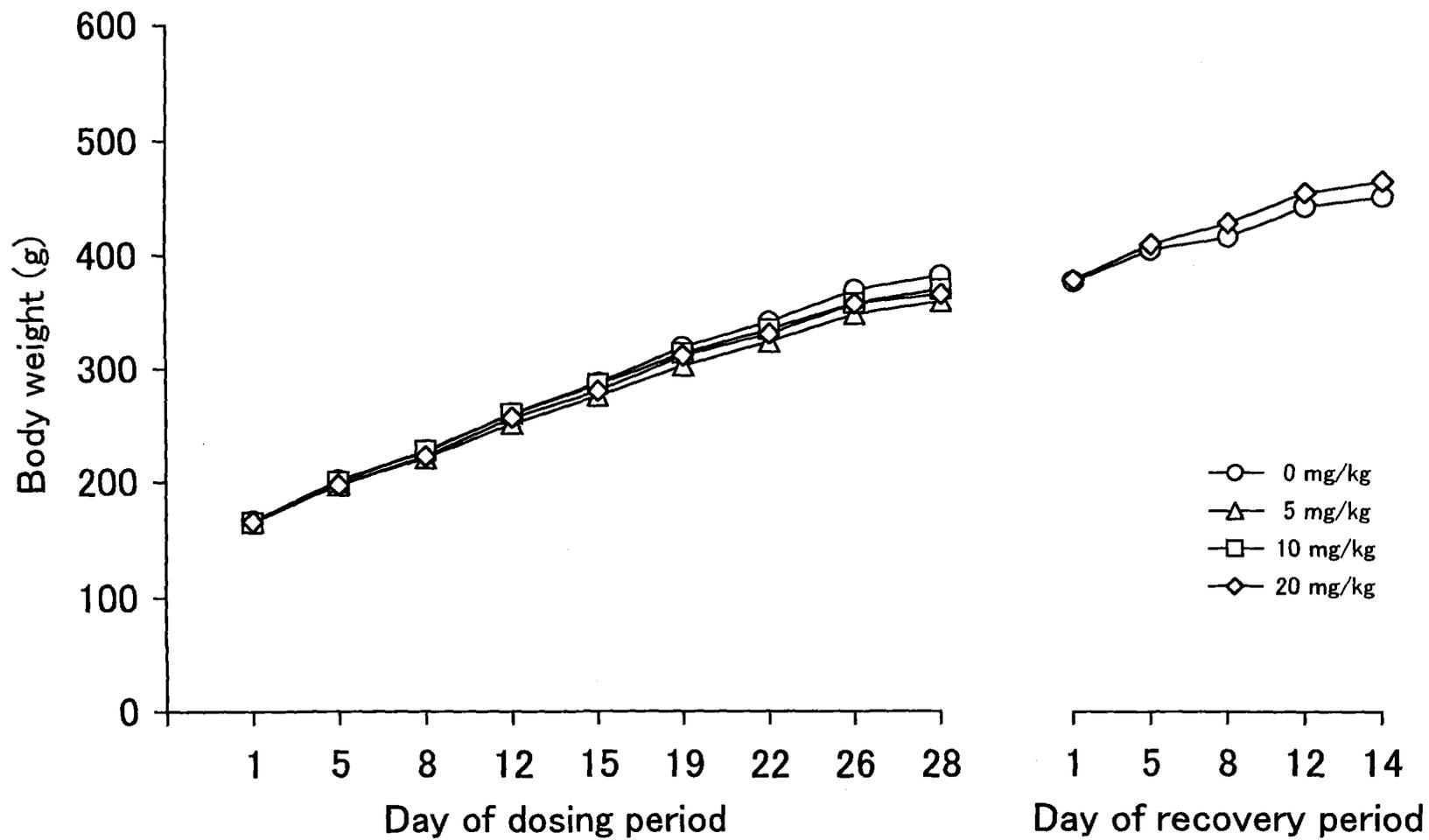


Fig. 1-1
Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats
Body weight changes in males

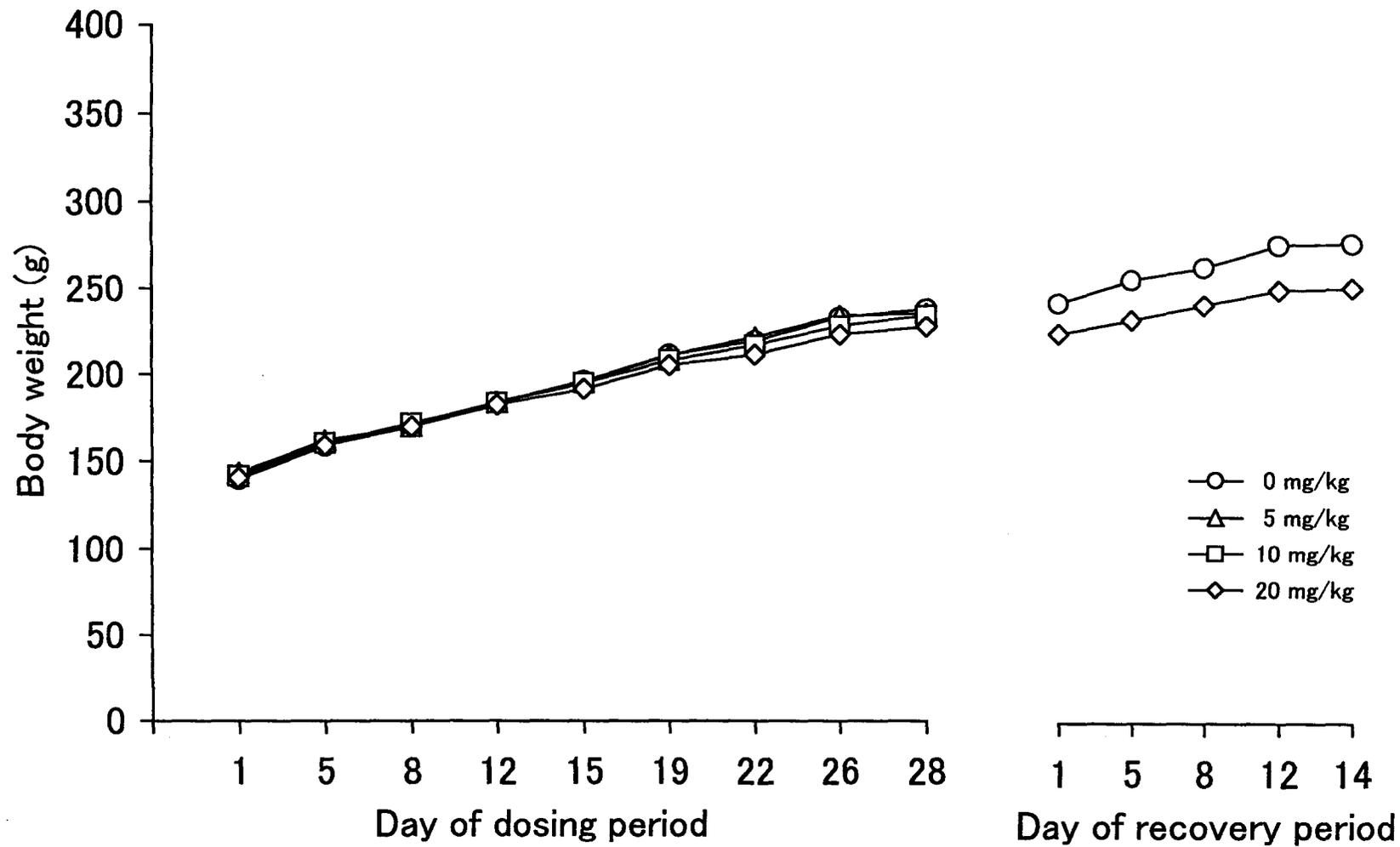


Fig. 1-2
Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in females

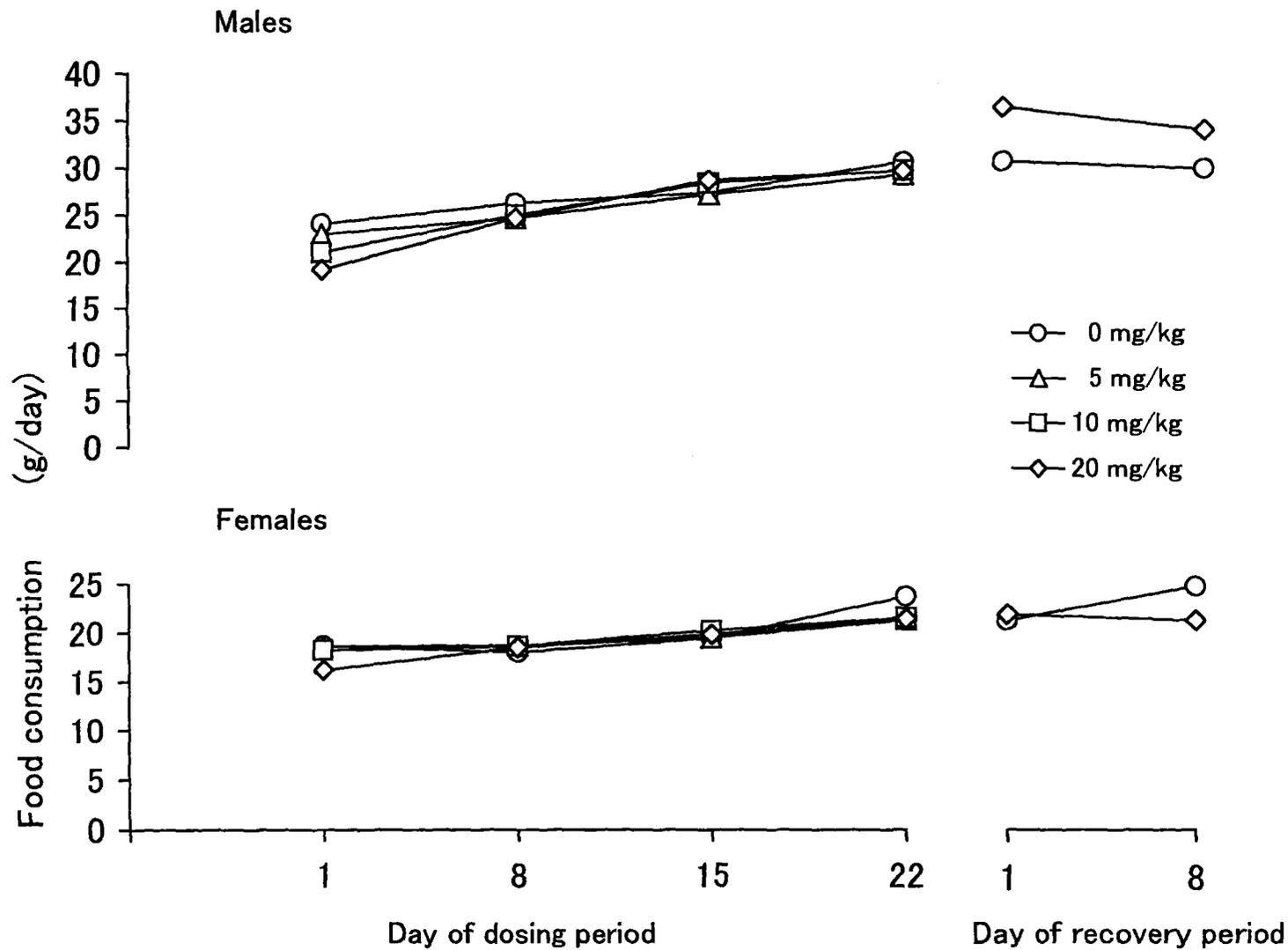


Fig. 2
Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in males and females

Table 1
Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in males

Clinical signs	Dose (mg/kg)	Initial number of animals	Number of animals with clinical signs																												Day of recovery period ^{a)} 1~14	Total		
			Day of dosing period																															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28				
Salivation occurred just after administration (disappeared within about one hour)	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	5	-	-	-	-	-	-	-	1	1	-	-	1	2	1	1	-	1	1	1	1	2	1	1	1	2	2	-	1	-	-	4	
	20	10	-	-	-	-	-	2	2	3	3	2	1	4	5	2	5	3	4	4	3	-	3	4	5	4	2	5	3	3	-	-	8	
Salivation occurred just after administration (continuously observed for about one hour or more)	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	10	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	-	-	1	-	-	1		
	20	10	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	2	1	1	2	4	2	1	2	1	3	2	2	2	-	-	5	
Discoloration of eyeball (unilateral)	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
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Clinical signs in females

Clinical signs	Dose (mg/kg)	Initial number of animals	Number of animals with clinical signs																												Day of recovery period ^{a)} 1~14	Total	
			Day of dosing period																														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28			
Salivation occurred just after administration (disappeared within about one hour)	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	5	-	-	-	-	-	-	-	-	1	-	1	1	1	3	2	3	1	1	-	1	-	1	1	2	2	2	2	1	-	-	5
	20	10	-	-	-	-	-	1	5	7	6	2	2	6	5	3	7	4	5	7	4	3	2	5	7	3	3	4	4	4	-	-	9
Salivation occurred just after administration (continuously observed for about one hour or more)	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	20	10	-	-	-	-	-	-	-	-	-	-	-	2	2	-	4	1	-	2	3	4	1	-	3	3	2	2	2	-	-	6	
Salivation was observed about one hour after administration or later	0	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	5	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	10	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	20	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1

a), recovery test was performed in 5 animals of the 0-mg/kg and 20-mg/kg group of both sexes.

-, no animal showed the sign.

Table 2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in males

Dose (mg/kg)	Day of dosing period									Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14
0	(10) 166.5 ±3.7	(10) 201.2 ±5.6	(10) 225.9 ±8.4	(10) 260.0 ±11.3	(10) 286.8 ±13.0	(10) 318.3 ±12.4	(10) 340.6 ±13.7	(10) 369.1 ±14.0	(10) 381.9 ±17.0	(5) 376.5 ±13.2	(5) 404.4 ±16.4	(5) 415.8 ±18.5	(5) 442.4 ±20.2	(5) 451.1 ±23.0
5	(5) 165.6 ±1.4	(5) 197.1 ±4.2	(5) 220.4 ±4.7	(5) 251.1 ±7.3	(5) 275.5 ±9.5	(5) 302.3 ±15.8	(5) 323.1 ±19.8	(5) 347.5 ±24.3	(5) 359.0 ±26.0					
10	(5) 164.8 ±3.9	(5) 199.4 ±6.1	(5) 226.8 ±7.5	(5) 259.9 ±9.3	(5) 285.6 ±10.5	(5) 313.1 ±12.5	(5) 334.1 ±15.1	(5) 357.5 ±12.4	(5) 369.6 ±14.4					
20	(10) 165.8 ±4.2	(10) 197.0 ±6.6	(10) 222.2 ±7.6	(10) 256.3 ±12.2	(10) 279.8 ±14.8	(10) 311.2 ±17.3	(10) 330.3 ±21.2	(10) 357.1 ±26.0	(10) 365.4 ±28.3	(5) 378.3 ±34.2	(5) 409.3 ±30.8	(5) 428.0 ±32.7	(5) 454.4 ±32.0	(5) 464.5 ±33.2

Parameter, mean(g)±S.D.
() . number of animals

Table 2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in females

Dose (mg/kg)	Day of dosing period									Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14
0	(10) 140.0 ±3.5	(10) 158.8 ±4.7	(10) 170.3 ±7.5	(10) 183.5 ±8.2	(10) 196.1 ±6.7	(10) 211.2 ±8.9	(10) 219.1 ±8.7	(10) 232.9 ±9.9	(10) 238.0 ±11.8	(5) 240.8 ±9.6	(5) 254.8 ±10.3	(5) 261.8 ±10.4	(5) 274.8 ±15.4	(5) 275.7 ±14.2
5	(5) 143.5 ±6.3	(5) 161.9 ±9.4	(5) 170.1 ±13.7	(5) 184.1 ±17.8	(5) 195.5 ±16.9	(5) 211.0 ±20.5	(5) 221.4 ±25.1	(5) 234.0 ±28.2	(5) 235.6 ±28.3					
10	(5) 141.9 ±5.3	(5) 160.4 ±6.7	(5) 171.7 ±8.5	(5) 183.6 ±10.5	(5) 194.9 ±16.8	(5) 208.3 ±19.1	(5) 216.6 ±21.1	(5) 227.9 ±23.0	(5) 234.3 ±22.2					
20	(10) 141.0 ±5.9	(10) 159.0 ±7.8	(10) 169.8 ±8.8	(10) 182.3 ±11.4	(10) 191.4 ±12.5	(10) 205.2 ±15.4	(10) 211.3 ±15.2	(10) 223.0 ±18.0	(10) 227.7 ±21.0	(5) 223.1 ±22.7	(5) 231.1 ±25.1	(5) 240.0 ±29.4	(5) 248.7 ±30.4	(5) 250.1 ±29.1

Parameter, mean(g)±S.D.
(), number of animals

Table 3-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in males

Dose (mg/kg)	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
0	(10) 24.0 ±2.0	(10) 26.2 ±1.9	(10) 27.3 ±2.4	(10) 30.6 ±2.2	(5) 31.1 ±2.0	(5) 30.3 ±2.1
5	(5) 22.9 ±0.8	(5) 24.6 ±2.0	(5) 27.1 ±1.7	(5) 29.2 ±3.0		
10	(5) 21.0* ±1.3	(5) 24.9 ±1.9	(5) 28.3 ±1.7	(5) 29.7 ±1.5		
20	(10) 19.1** ±2.0	(10) 24.6 ±1.9	(10) 28.6 ±5.9	(10) 29.6 ±3.6	(5) 37.0* ±4.9	(5) 34.5 ±3.8

Parameter, mean(g)±S.D.
(), number of animals

*. significantly different from control, p<0.05
**. significantly different from control, p<0.01

Table 3-2
 Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats
 Food consumption in females

Dose (mg/kg)	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
0	(10) 18.7 ±1.5	(10) 18.0 ±1.5	(10) 19.4 ±1.7	(10) 23.7 ±2.0	(5) 21.3 ±3.0	(5) 24.8 ±1.6
5	(5) 18.6 ±1.7	(5) 18.7 ±0.9	(5) 19.5 ±2.8	(5) 21.3 ±3.0		
10	(5) 18.2 ±2.5	(5) 18.6 ±2.2	(5) 20.2 ±1.9	(5) 21.5 ±3.7		
20	(10) 16.2** ±1.2	(10) 18.5 ±1.8	(10) 19.8 ±3.0	(10) 21.4 ±1.8	(5) 21.9 ±1.6	(5) 21.3 ±5.6

Parameter, mean(g)±S.D.
 (), number of animals

** , significantly different from control, p<0.01

Table 4-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in males and females on day 26 of dosing period

Sex	Dose (mg/kg)	Number of animals	Color ^{a)}	Turbidity ^{b)}	pH						Protein ^{c)}			Glucose ^{d)}			Ketone ^{b)}			Bilirubin ^{b)}			Occult blood ^{b)}			Urobilinogen ^{e)}	
			ly	-	6.5	7.0	7.5	8.0	8.5	≥9.0	-	±	+	-	-	±	+	-	-	±	+	±	+				
Male	0	10	10	10	0	3	4	1	1	1	0	2	8	10	4	5	1	10	10	0	0	10	0				
	5	5	5	5	0	1	1	2	1	0	0	1	4	5	1	4	0	5	5	0	0	5	0				
	10	5	5	5	0	0	2	2	1	0	0	2	3	5	1	3	1	5	4	0	1	5	0				
	20	10	10	10	0	3	3	0	1	3	0	0	10	10	2	6	2	10	10	0	0	9	1				
Female	0	10	10	10	1	6	3	0	0	0	5	5	0	10	9	1	0	10	10	0	0	9	1				
	5	5	5	5	0	2	1	0	1	1	5	0	0	5	5	0	0	5	5	0	0	5	0				
	10	5	5	5	0	1	3	1	0	0	5	0	0	5	5	0	0	5	5	0	0	5	0				
	20	10	10	10	2	2	4	2	0	0	10	0	0	10	9	1	0	10	10	0	0	8	2				

a) ly, light yellow

b) -, negative; ±, trace; +, slight

c) -, negative; ±, trace; +, 30 mg/dL

d) -, negative

e) ±, 0.1 E.U./dL; +, 1.0 E.U./dL

Table 4-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in males and females on day 26 of dosing period

Sex	Dose (mg/kg)	Number of animals	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
					Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
Male	0	10	26.9 ±10.9	1.038 ± 0.011	82.2 ± 23.7	176.1 ± 54.2	101.5 ± 34.9	2.00 ± 0.22	4.23 ± 0.71	2.41 ± 0.36	0.48 ± 0.10
	5	5	24.9 ± 4.6	1.033 ± 0.007	71.3 ± 23.9	174.3 ± 38.4	91.4 ± 26.9	1.75 ± 0.60	4.26 ± 0.89	2.24 ± 0.68	0.40 ± 0.07
	10	5	27.1 ± 2.8	1.030 ± 0.005	60.8 ± 13.5	154.2 ± 23.9	81.9 ± 15.5	1.62 ± 0.27	4.13 ± 0.33	2.20 ± 0.35	0.39 ± 0.05
	20	10	24.0 ± 5.3	1.033 ± 0.007	76.2 ± 18.2	173.7 ± 30.5	104.4 ± 20.8	1.77 ± 0.39	4.06 ± 0.71	2.44 ± 0.46	0.44 ± 0.06
Female	0	10	14.9 ± 4.8	1.036 ± 0.008	83.2 ± 23.9	200.2 ± 41.2	100.0 ± 28.0	1.22 ± 0.43	2.93 ± 0.84	1.48 ± 0.55	0.41 ± 0.07
	5	5	17.5 ± 4.3	1.032 ± 0.012	76.3 ± 28.9	172.9 ± 61.7	88.8 ± 39.1	1.26 ± 0.43	2.83 ± 0.75	1.43 ± 0.55	0.44 ± 0.05
	10	5	17.7 ± 4.1	1.034 ± 0.004	76.2 ± 15.2	181.0 ± 17.3	98.2 ± 4.9	1.38 ± 0.47	3.16 ± 0.60	1.74 ± 0.40	0.43 ± 0.09
	20	10	19.6 ± 5.7	1.031 ± 0.011	63.6 ± 21.4	162.9 ± 49.5	88.3 ± 30.8	1.19 ± 0.41	3.03 ± 0.73	1.66 ± 0.57	0.39 ± 0.05

Parameter, mean±S. D.

Table 4-2
Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in males and females on day 12 of recovery period

Sex	Dose (mg/kg)	Number of animals	Color ^{a)}		pH						Protein ^{c)}			Glucose ^{d)}			Ketone ^{b)}			Bilirubin ^{b)}		Occult blood ^{b)}		Urobilinogen ^{e)}	
			ly	-	6.5	7.0	7.5	8.0	8.5	≥9.0	-	±	+	-	-	±	+	-	-	±	+				
Male	0	5	5	5	0	0	2	2	1	0	1	1	3	5	1	3	1	5	5	5	0				
	20	5	5	5	0	0	1	2	2	0	1	0	4	5	1	3	1	5	5	4	1				
Female	0	5	5	5	0	3	0	0	1	1	4	1	0	5	5	0	0	5	5	5	0				
	20	5	5	5	1	1	3	0	0	0	4	1	0	5	4	1	0	5	5	4	1				

a) ly, light yellow
b) -, negative; ±, trace; +, slight
c) -, negative; ±, trace; +, 30 mg/dL
d) -, negative
e) ±, 0.1 E. U. /dL; +, 1.0 E. U. /dL

Table 4-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in males and females on day 12 of recovery period

Sex	Dose (mg/kg)	Number of animals	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
					Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
Male	0	5	32.9 ±11.0	1.033 ± 0.010	75.9 ± 27.9	141.9 ± 47.8	82.8 ± 34.2	2.27 ± 0.22	4.28 ± 0.53	2.46 ± 0.42	0.53 ± 0.03
	20	5	26.6 ± 3.7	1.040 ± 0.008	103.4 ± 21.8	188.7 ± 27.1	116.2 ± 19.1	2.69* ± 0.24	4.94* ± 0.23	3.04* ± 0.19	0.54 ± 0.05
Female	0	5	17.7 ± 1.8	1.037 ± 0.004	107.6 ± 9.3	187.8 ± 15.3	112.0 ± 12.7	1.90 ± 0.27	3.31 ± 0.27	1.98 ± 0.31	0.57 ± 0.04
	20	5	18.3 ± 6.1	1.034 ± 0.005	101.4 ± 16.7	177.0 ± 23.8	104.0 ± 13.9	1.79 ± 0.41	3.16 ± 0.85	1.88 ± 0.61	0.57 ± 0.03

Parameter, mean±S.D.

*, significantly different from control, p<0.05

Table 5-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in males at the end of dosing period

Dose (mg/kg)	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
0	(5) 71.7 ± 3.2	(5) 14.7 ± 0.4	(5) 43.0 ± 1.5	(5) 60.0 ± 1.4	(5) 20.6 ± 0.7	(5) 34.3 ± 0.5	(5) 3.7 ± 0.4	(5) 103.7 ± 7.0	(5) 18.7 ± 2.0	(5) 21.1 ± 1.4
5	(5) 70.0 ± 2.8	(5) 14.8 ± 0.5	(5) 42.9 ± 1.6	(5) 61.4 ± 1.3	(5) 21.2 ± 0.5	(5) 34.6 ± 0.7	(5) 3.2 ± 0.2	(5) 95.1 ± 5.3	(5) 20.2 ± 3.0	(5) 21.0 ± 2.0
10	(5) 70.0 ± 3.5	(5) 14.7 ± 0.6	(5) 42.3 ± 1.9	(5) 60.5 ± 0.5	(5) 21.0 ± 0.4	(5) 34.7 ± 0.5	(5) 3.3 ± 1.6	(5) 102.1 ± 7.5	(5) 17.3 ± 2.0	(5) 20.4 ± 0.9
20	(5) 70.1 ± 4.0	(5) 15.0 ± 0.6	(5) 42.6 ± 1.8	(5) 60.8 ± 1.2	(5) 21.4 ± 0.4	(5) 35.2 ± 0.7	(5) 3.3 ± 0.8	(5) 102.1 ± 5.3	(5) 14.2* ± 1.2	(5) 18.4 ± 2.0

Dose (mg/kg)	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
0	(5) 75 ± 2.3	(5) 0 ± 0	(5) 15 ± 8	(5) 1 ± 2	(5) 0 ± 0	(5) 3 ± 4	(5) 81 ± 11
5	(5) 81 ± 1.5	(5) 0 ± 0	(5) 6 ± 5	(5) 1 ± 1	(5) 0 ± 0	(5) 2 ± 2	(5) 90 ± 5
10	(5) 76 ± 3.1	(5) 0 ± 0	(5) 7 ± 4	(5) 1 ± 1	(5) 0 ± 0	(5) 2 ± 2	(5) 89 ± 7
20	(5) 77 ± 2.0	(5) 0 ± 0	(5) 7 ± 5	(5) 0 ± 1	(5) 0 ± 0	(5) 2 ± 1	(5) 90 ± 5

Parameter, mean \pm S.D.
(), number of animals*, significantly different from control, $p < 0.05$

Table 5-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in females at the end of dosing period

Dose (mg/kg)	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
0	(5) 714 ± 23	(5) 14.9 ± 0.5	(5) 42.8 ± 1.4	(5) 60.0 ± 0.9	(5) 20.9 ± 0.3	(5) 34.8 ± 0.4	(5) 2.4 ± 1.0	(5) 88.3 ± 6.4	(5) 12.0 ± 0.6	(5) 16.9 ± 1.4
5	(5) 709 ± 23	(5) 14.6 ± 0.2	(5) 41.5 ± 0.9	(5) 58.6 ± 1.7	(5) 20.7 ± 0.8	(5) 35.3 ± 1.0	(5) 2.1 ± 0.7	(5) 96.8 ± 9.2	(5) 12.5 ± 0.8	(5) 16.3 ± 0.7
10	(5) 711 ± 27	(5) 14.8 ± 0.5	(5) 42.9 ± 1.7	(5) 60.4 ± 1.8	(5) 20.8 ± 0.4	(5) 34.5 ± 0.5	(5) 2.2 ± 0.9	(5) 105.7 ± 7.8	(5) 12.9 ± 0.2	(5) 15.0 ± 1.6
20	(5) 714 ± 43	(5) 14.8 ± 0.6	(5) 42.5 ± 1.8	(5) 59.6 ± 2.5	(5) 20.8 ± 0.8	(5) 35.0 ± 0.7	(5) 1.9 ± 0.4	(5) 96.8 ± 14.4	(5) 12.7 ± 0.5	(5) 15.7 ± 1.1

Dose (mg/kg)	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
0	(5) 47 ± 12	(5) 0 ± 0	(5) 8 ± 3	(5) 1 ± 1	(5) 0 ± 0	(5) 3 ± 2	(5) 89 ± 4
5	(5) 49 ± 18	(5) 0 ± 0	(5) 8 ± 6	(5) 1 ± 1	(5) 0 ± 0	(5) 1 ± 1	(5) 90 ± 5
10	(5) 44 ± 4	(5) 0 ± 0	(5) 14 ± 8	(5) 1 ± 1	(5) 0 ± 0	(5) 2 ± 1	(5) 84 ± 9
20	(5) 42 ± 5	(5) 0 ± 0	(5) 8 ± 5	(5) 0 ± 1	(5) 0 ± 0	(5) 1 ± 1	(5) 91 ± 6

Parameter, mean \pm S.D.
(), number of animals

Table 5-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in males at the end of recovery period

Dose (mg/kg)	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
0	(5) 777 ± 26	(5) 15.2 ± 0.4	(5) 44.6 ± 1.8	(5) 57.4 ± 0.7	(5) 19.6 ± 0.3	(5) 34.1 ± 0.8	(5) 1.7 ± 0.4	(5) 104.6 ± 10.2	(5) 15.9 ± 2.6	(5) 20.6 ± 2.0
20	(5) 735* ± 21	(5) 15.1 ± 0.3	(5) 43.5 ± 1.1	(5) 59.2** ± 0.9	(5) 20.6** ± 0.5	(5) 34.7 ± 0.3	(5) 2.8* ± 0.9	(5) 89.5* ± 8.3	(5) 15.5 ± 2.5	(5) 19.3 ± 1.5

Dose (mg/kg)	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
0	(5) 88 ± 23	(5) 0 ± 0	(5) 4 ± 2	(5) 0 ± 0	(5) 0 ± 0	(5) 2 ± 2	(5) 94 ± 1
20	(5) 67 ± 8	(5) 0 ± 0	(5) 9 ± 6	(5) 0 ± 0	(5) 0 ± 0	(5) 5 ± 2	(5) 86 ± 6

Parameter, mean \pm S.D.
(), number of animals

*, significantly different from control, $p < 0.05$
**, significantly different from control, $p < 0.01$

Table 5-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in females at the end of recovery period

Dose (mg/kg)	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
0	(5) 775 ± 18	(5) 15.3 ± 0.3	(5) 44.4 ± 1.1	(5) 57.3 ± 0.9	(5) 19.8 ± 0.2	(5) 34.6 ± 0.5	(5) 2.4 ± 0.6	(5) 95.3 ± 10.6	(5) 12.0 ± 0.5	(5) 17.5 ± 1.0
20	(5) 740* ± 16	(5) 14.9* ± 0.3	(5) 43.0 ± 1.1	(5) 58.1 ± 1.5	(5) 20.1 ± 0.6	(5) 34.6 ± 0.5	(5) 2.6 ± 0.4	(5) 91.0 ± 6.8	(5) 11.7 ± 0.5	(5) 15.9* ± 0.7

Dose (mg/kg)	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
0	(5) 45 ± 7	(5) 0 ± 0	(5) 7 ± 3	(5) 0 ± 1	(5) 0 ± 0	(5) 4 ± 2	(5) 89 ± 4
20	(5) 39 ± 10	(5) 0 ± 0	(5) 9 ± 6	(5) 1 ± 1	(5) 0 ± 0	(5) 3 ± 3	(5) 87 ± 8

Parameter, mean \pm S.D.
(), number of animals*, significantly different from control, $p < 0.05$

Table 6-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in males at the end of dosing period

Dose (mg/kg)	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri- glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
0	(5) 5.2 ±0.2	(5) 3.0 ±0.1	(5) 1.36 ±0.13	(5) 133 ±7	(5) 40 ±4	(5) 41 ±4	(5) 17 ±3	(5) 0.5 ±0.0	(5) 7.5 ±0.4	(5) 8.9 ±0.2
5	(5) 5.1 ±0.2	(5) 3.0 ±0.2	(5) 1.37 ±0.21	(5) 125 ±3	(5) 36 ±6	(5) 42 ±10	(5) 16 ±2	(5) 0.5 ±0.1	(5) 7.4 ±0.2	(5) 8.9 ±0.2
10	(5) 5.3 ±0.2	(5) 3.0 ±0.2	(5) 1.30 ±0.12	(5) 126 ±6	(5) 43 ±6	(5) 43 ±18	(5) 16 ±4	(5) 0.6 ±0.1	(5) 7.5 ±0.3	(5) 8.9 ±0.2
20	(5) 5.3 ±0.3	(5) 3.2 ±0.1	(5) 1.47 ±0.10	(5) 130 ±10	(5) 44 ±5	(5) 37 ±5	(5) 17 ±2	(5) 0.6 ±0.0	(5) 7.3 ±0.6	(5) 9.0 ±0.1

Dose (mg/kg)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
0	(5) 145.6 ±0.7	(5) 3.52 ±0.15	(5) 107.4 ±1.1	(5) 453 ±62	(5) 29 ±5	(5) 69 ±5	(5) 0 ±0
5	(5) 145.0 ±0.7	(5) 3.61 ±0.12	(5) 107.2 ±1.1	(5) 425 ±99	(5) 29 ±1	(5) 66 ±6	(5) 0 ±0
10	(5) 144.8 ±0.3	(5) 3.73 ±0.23	(5) 107.4 ±1.3	(5) 396 ±66	(5) 29 ±3	(5) 61 ±6	(5) 0 ±0
20	(5) 145.2 ±0.6	(5) 3.63 ±0.20	(5) 108.3 ±1.2	(5) 399 ±80	(5) 34 ±7	(5) 67 ±13	(5) 0 ±0

Parameter, mean±S.D.
(), number of animals

Table 6-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in females at the end of dosing period

Dose (mg/kg)	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri- glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. phos. (mg/dL)	Ca (mg/dL)
0	(5) 5.2 ±0.2	(5) 3.2 ±0.1	(5) 1.58 ±0.11	(5) 125 ±10	(5) 50 ±4	(5) 30 ±7	(5) 16 ±2	(5) 0.6 ±0.0	(5) 5.8 ±0.8	(5) 8.7 ±0.2
5	(5) 5.4 ±0.2	(5) 3.3 ±0.1	(5) 1.66 ±0.14	(5) 122 ±10	(5) 51 ±6	(5) 30 ±6	(5) 19 ±3	(5) 0.6 ±0.0	(5) 6.6 ±0.6	(5) 8.9 ±0.2
10	(5) 5.1 ±0.2	(5) 3.2 ±0.2	(5) 1.66 ±0.14	(5) 120 ±10	(5) 52 ±13	(5) 31 ±7	(5) 16 ±3	(5) 0.6 ±0.0	(5) 5.8 ±1.0	(5) 8.6 ±0.4
20	(5) 4.9 ±0.3	(5) 3.1 ±0.2	(5) 1.66 ±0.12	(5) 118 ±6	(5) 56 ±10	(5) 30 ±13	(5) 19 ±4	(5) 0.6 ±0.1	(5) 6.3 ±0.2	(5) 8.6 ±0.2

Dose (mg/kg)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
0	(5) 143 ±0.9	(5) 3.26 ±0.19	(5) 108 ±0.8	(5) 259 ±91	(5) 20 ±2	(5) 62 ±5	(5) 0 ±1
5	(5) 143 ±1.3	(5) 3.47 ±0.29	(5) 108 ±1.3	(5) 244 ±83	(5) 24 ±3	(5) 57 ±4	(5) 0 ±0
10	(5) 144 ±0.9	(5) 3.38 ±0.19	(5) 109 ±1.7	(5) 276 ±65	(5) 24 ±3	(5) 57 ±5	(5) 0 ±0
20	(5) 144 ±1.5	(5) 3.31 ±0.37	(5) 109 ±1.2	(5) 293 ±52	(5) 25 ±5	(5) 58 ±3	(5) 0 ±1

Parameter, mean±S.D.
(), number of animals

Table 6-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in males at the end of recovery period

Dose (mg/kg)	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri- glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
0	(5) 5.5 ±0.1	(5) 3.2 ±0.1	(5) 1.39 ±0.12	(5) 167 ±40	(5) 46 ±11	(5) 48 ±9	(5) 15 ±3	(5) 0.7 ±0.1	(5) 7.4 ±0.5	(5) 8.9 ±0.2
20	(5) 5.2** ±0.1	(5) 3.1 ±0.1	(5) 1.50 ±0.12	(5) 147 ±15	(5) 40 ±6	(5) 50 ±11	(5) 14 ±2	(5) 0.6 ±0.1	(5) 7.1 ±0.5	(5) 9.0 ±0.2

Dose (mg/kg)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
0	(5) 145.3 ±1.4	(5) 4.03 ±0.44	(5) 106.5 ±1.1	(5) 319 ±53	(5) 30 ±6	(5) 70 ±7	(5) 0 ±0
20	(5) 145.1 ±0.7	(5) 3.61 ±0.25	(5) 106.2 ±0.5	(5) 309 ±49	(5) 30 ±2	(5) 70 ±6	(5) 0 ±0

Parameter, mean±S.D.
(), number of animals

**, significantly different from control, p<0.01

Table 6-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in females at the end of recovery period

Dose (mg/kg)	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri- glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
0	(5) 5.8 ±0.3	(5) 3.6 ±0.3	(5) 1.61 ±0.25	(5) 130 ±14	(5) 53 ±10	(5) 41 ±22	(5) 21 ±3	(5) 0.7 ±0.1	(5) 6.0 ±0.7	(5) 9.1 ±0.3
20	(5) 5.6 ±0.2	(5) 3.4 ±0.2	(5) 1.61 ±0.13	(5) 119 ±14	(5) 62 ±4	(5) 27 ±10	(5) 20 ±2	(5) 0.7 ±0.0	(5) 6.2 ±0.8	(5) 8.9 ±0.3

Dose (mg/kg)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
0	(5) 144.2 ±1.2	(5) 4.04 ±0.31	(5) 107.5 ±2.5	(5) 186 ±16	(5) 24 ±3	(5) 64 ±8	(5) 1 ±0
20	(5) 145.2 ±1.3	(5) 3.89 ±0.35	(5) 108.9 ±0.9	(5) 191 ±42	(5) 26 ±7	(5) 65 ±14	(5) 0 ±0

Parameter, mean±S.D.
(), number of animals

Table 7-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in males at the end of dosing period

Dose (mg/kg)	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Spleen (mg)	Adrenal glands (mg)	Testes (mg)	Epididymides (mg)
0	(5) 348.7 ±16.9	(5) 1896.4 ±64.6	(5) 621.5 ±90.5	(5) 1259.9 ±78.8	(5) 10540.8 ±708.4	(5) 2623.6 ±147.5	(5) 723.7 ±71.2	(5) 58.9 ±12.9	(5) 3159.3 ±294.7	(5) 722.8 ±29.5
5	(5) 326.1 ±23.9	(5) 1916.0 ±82.1	(5) 580.8 ±111.9	(5) 1086.4* ±77.3	(5) 9927.4 ±910.4	(5) 2444.1 ±187.2	(5) 669.1 ±111.1	(5) 45.6 ±5.2	(5) 2942.5 ±122.6	(5) 695.3 ±11.4
10	(5) 334.0 ±15.4	(5) 1923.2 ±55.9	(5) 641.3 ±162.3	(5) 1077.0** ±104.8	(5) 10202.5 ±338.4	(5) 2449.7 ±168.9	(5) 670.0 ±127.6	(5) 49.6 ±3.4	(5) 3030.4 ±128.5	(5) 707.6 ±51.1
20	(5) 325.7 ±16.8	(5) 1919.2 ±123.1	(5) 540.3 ±92.1	(5) 1043.6** ±65.4	(5) 9943.1 ±1170.0	(5) 2473.4 ±191.5	(5) 653.0 ±127.0	(5) 55.2 ±7.0	(5) 2949.1 ±158.0	(5) 696.0 ±50.0

Parameter, mean±S.D.
(), number of animals

*. significantly different from control, p<0.05
**. significantly different from control, p<0.01

Table 7-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in females at the end of dosing period

Dose (mg/kg)	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Spleen (mg)	Adrenal glands (mg)	Ovaries (mg)
0	(5) 214.7 ±10.8	(5) 1805.3 ±70.2	(5) 499.0 ±71.5	(5) 771.3 ±59.3	(5) 6499.5 ±275.6	(5) 1713.7 ±80.4	(5) 521.8 ±13.2	(5) 61.5 ±8.7	(5) 87.9 ±12.3
5	(5) 213.6 ±25.4	(5) 1727.2 ±69.2	(5) 503.9 ±108.3	(5) 748.4 ±106.6	(5) 6351.2 ±1132.3	(5) 1649.4 ±222.2	(5) 610.0 ±212.5	(5) 57.3 ±12.2	(5) 84.4 ±17.1
10	(5) 213.2 ±21.0	(5) 1755.5 ±65.6	(5) 442.2 ±92.1	(5) 724.3 ±54.3	(5) 6120.9 ±881.6	(5) 1550.7 ±72.2	(5) 502.5 ±95.5	(5) 55.0 ±6.1	(5) 77.1 ±10.3
20	(5) 211.0 ±18.8	(5) 1742.6 ±92.8	(5) 446.8 ±62.9	(5) 763.0 ±100.9	(5) 6595.1 ±803.4	(5) 1602.6 ±135.1	(5) 452.4 ±88.2	(5) 60.1 ±4.3	(5) 85.9 ±11.4

Parameter, mean±S.D.
(), number of animals

Table 7-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in males at the end of recovery period

Dose (mg/kg)	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Spleen (mg)	Adrenal glands (mg)	Testes (mg)	Epididymides (mg)
0	410.5 ±19.3 (5)	1976.7 ±62.4 (5)	545.7 ±131.1 (5)	1230.1 ±52.8 (5)	11831.7 ±963.2 (5)	2749.4 ±274.7 (5)	755.6 ±68.0 (5)	55.7 ±3.9 (5)	3223.9 ±395.3 (5)	953.6 ±168.5 (5)
20	424.3 ±30.6 (5)	1986.9 ±11.8 (5)	529.6 ±76.4 (5)	1254.6 ±117.5 (5)	12920.9 ±1257.9 (5)	2839.4 ±196.4 (5)	881.0 ±111.5 (5)	54.9 ±5.8 (5)	3300.5 ±266.6 (5)	1067.5 ±58.9 (5)

Parameter, mean±S.D.
(), number of animals

Table 7-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in females at the end of recovery period

Dose (mg/kg)	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Spleen (mg)	Adrenal glands (mg)	Ovaries (mg)
0	251.7 ±14.5 (5)	1855.1 ±98.4 (5)	392.9 ±55.3 (5)	815.5 ±48.7 (5)	7001.4 ±563.2 (5)	1752.9 ±88.7 (5)	506.9 ±66.7 (5)	58.8 ±8.7 (5)	83.4 ±17.7 (5)
20	226.2 ±26.3 (5)	1839.6 ±108.9 (5)	388.9 ±88.2 (5)	799.1 ±97.5 (5)	6677.6 ±1024.8 (5)	1657.1 ±292.5 (5)	503.3 ±139.3 (5)	62.7 ±7.8 (5)	79.8 ±18.6 (5)

Parameter, mean±S.D.
(), number of animals

Table 8-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in males at the end of dosing period

Dose (mg/kg)	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Spleen (mg/g)	Adrenal glands (mg/g)	Testes (mg/g)	Epididymides (mg/g)
0	(5) 348.7 ±16.9	(5) 5.450 ±0.360	(5) 1.778 ±0.205	(5) 3.618 ±0.257	(5) 30.227 ±1.290	(5) 7.538 ±0.568	(5) 2.082 ±0.248	(5) 0.170 ±0.041	(5) 9.083 ±0.999	(5) 2.079 ±0.163
5	(5) 326.1 ±23.9	(5) 5.895 ±0.414	(5) 1.786 ±0.345	(5) 3.336 ±0.188	(5) 30.411 ±0.703	(5) 7.514 ±0.635	(5) 2.047 ±0.284	(5) 0.140 ±0.014	(5) 9.074 ±0.917	(5) 2.140 ±0.145
10	(5) 334.0 ±15.4	(5) 5.765 ±0.266	(5) 1.912 ±0.439	(5) 3.223* ±0.255	(5) 30.572 ±1.119	(5) 7.337 ±0.456	(5) 2.008 ±0.393	(5) 0.149 ±0.011	(5) 9.086 ±0.527	(5) 2.120 ±0.140
20	(5) 325.7 ±16.8	(5) 5.892 ±0.200	(5) 1.658 ±0.262	(5) 3.207* ±0.195	(5) 30.461 ±2.355	(5) 7.594 ±0.430	(5) 2.000 ±0.331	(5) 0.169 ±0.015	(5) 9.058 ±0.319	(5) 2.140 ±0.161

Parameter, mean±S.D.
(), number of animals

*, significantly different from control. p<0.05

Table 8-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in females at the end of dosing period

Dose (mg/kg)	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Spleen (mg/g)	Adrenal glands (mg/g)	Ovaries (mg/g)
0	(5) 214.7 ±10.8	(5) 8.416 ±0.286	(5) 2.322 ±0.290	(5) 3.594 ±0.235	(5) 30.291 ±0.701	(5) 7.988 ±0.283	(5) 2.438 ±0.175	(5) 0.285 ±0.028	(5) 0.408 ±0.043
5	(5) 213.6 ±25.4	(5) 8.168 ±0.915	(5) 2.340 ±0.282	(5) 3.498 ±0.154	(5) 29.593 ±2.103	(5) 7.714 ±0.323	(5) 2.799 ±0.710	(5) 0.267 ±0.036	(5) 0.392 ±0.037
10	(5) 213.2 ±21.0	(5) 8.302 ±0.906	(5) 2.097 ±0.518	(5) 3.409 ±0.221	(5) 28.670 ±2.220	(5) 7.318 ±0.643	(5) 2.344 ±0.240	(5) 0.258 ±0.019	(5) 0.364 ±0.055
20	(5) 211.0 ±18.8	(5) 8.299 ±0.699	(5) 2.116 ±0.222	(5) 3.616 ±0.324	(5) 31.204 ±1.553	(5) 7.601 ±0.220	(5) 2.133 ±0.264	(5) 0.285 ±0.014	(5) 0.407 ±0.042

Parameter, mean±S.D.
(), number of animals

Table 8-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in males at the end of recovery period

Dose (mg/kg)	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Spleen (mg/g)	Adrenal glands (mg/g)	Testes (mg/g)	Epididymides (mg/g)
0	(5) 410.5 ±19.3	(5) 4.818 ±0.117	(5) 1.331 ±0.326	(5) 2.998 ±0.106	(5) 28.824 ±1.977	(5) 6.705 ±0.707	(5) 1.846 ±0.213	(5) 0.136 ±0.009	(5) 7.844 ±0.797	(5) 2.317 ±0.361
20	(5) 424.3 ±30.6	(5) 4.705 ±0.380	(5) 1.247 ±0.144	(5) 2.959 ±0.219	(5) 30.421 ±1.413	(5) 6.693 ±0.096	(5) 2.076 ±0.209	(5) 0.129 ±0.013	(5) 7.814 ±0.878	(5) 2.519 ±0.091

Parameter, mean±S.D.
(), number of animals

Table 8-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in females at the end of recovery period

Dose (mg/kg)	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Spleen (mg/g)	Adrenal glands (mg/g)	Ovaries (mg/g)
0	(5) 251.7 ±14.5	(5) 7.388 ±0.554	(5) 1.571 ±0.296	(5) 3.249 ±0.285	(5) 27.812 ±1.488	(5) 6.994 ±0.726	(5) 2.030 ±0.386	(5) 0.234 ±0.039	(5) 0.330 ±0.058
20	(5) 226.2 ±26.3	(5) 8.201 ±0.896	(5) 1.704 ±0.266	(5) 3.535 ±0.215	(5) 29.448 ±1.890	(5) 7.304 ±0.695	(5) 2.195 ±0.375	(5) 0.277 ±0.016	(5) 0.352 ±0.062

Parameter, mean±S.D.
(), number of animals

Table 9-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in males at the end of dosing period

Dose Grade	0 mg/kg		5 mg/kg		10 mg/kg		20 mg/kg	
	-	+	-	+	-	+	-	+
(Eye)	[5]		[5]		[5]		[5]	
Area, dark	5	0	5	0	4	1	5	0

-, negative; +, positive.

[], number of animals examined.

Table 9-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in females at the end of dosing period

Dose	0 mg/kg		5 mg/kg		10 mg/kg		20 mg/kg	
	-	+	-	+	-	+	-	+
(Kidney)	[5]		[5]		[5]		[5]	
Cyst	4	1	5	0	5	0	5	0
(Spleen)	[5]		[5]		[5]		[5]	
Small	5	0	5	0	5	0	4	1

-, negative; +, positive.

[], number of animals examined.

Table 9-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in males at the end of recovery period

Dose	0 mg/kg		20 mg/kg	
	-	+	-	+
Grade				
(Kidney)	[5]		[5]	
Enlargement	5	0	4	1
Area, pale, cortex	5	0	4	1
(Testis)	[5]		[5]	
Small, unilateral	4	1	5	0
(Epididymis)	[5]		[5]	
Small, unilateral	4	1	5	0

-, negative; +, positive.

[], number of animals examined.

Table 10-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in males at the end of dosing period

Dose Grade	0 mg/kg						5 mg/kg						10 mg/kg						20 mg/kg					
	-	±	+	++	+++	Pos.	-	±	+	++	+++	Pos.	-	±	+	++	+++	Pos.	-	±	+	++	+++	Pos.
(Kidney)	[5]						[5]						[5]						[5]					
Eosinophilic body, proximal tubule	5	0	0	0	0	0	5	0	0	0	0	0	5	0	0	0	0	0	3	0	2	0	0	2
Basophilic tubule	1	4	0	0	0	4	2	3	0	0	0	3	0	4	1	0	0	5	2	3	0	0	0	3
Cellular infiltration, lymphocyte	0	5	0	0	0	5	2	3	0	0	0	3	0	5	0	0	0	5	1	4	0	0	0	4
Cast, proteinous	3	2	0	0	0	2	5	0	0	0	0	0	4	1	0	0	0	1	4	0	1	0	0	1
(Spleen)	[5]												[5]											
Deposit, pigment, brown	0	0	5	0	0	5							0						0	5	0	0	5	
Hematopoiesis, extramedullary	0	3	2	0	0	5							0						4	0	1	0	5	
(Heart)	[5]												[5]											
Myocardial degeneration / fibrosis	4	1	0	0	0	1							4						0	1	0	0	1	
(Liver)	[5]												[5]											
No abnormalities																								
(Adrenal gland)	[5]												[5]											
No abnormalities																								
(Stomach)	[5]												[5]											
No abnormalities																								
(Testis)	[5]												[5]											
No abnormalities																								
(Epididymis)	[5]												[5]											
No abnormalities																								
(Eye)													[1]											
Hemorrhage, vitreous cavity													0						0	1	0	0	1	

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe; Pos., total of positive grade.

[], number of animals examined.

Table 10-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in females at the end of dosing period

Dose	0 mg/kg						20 mg/kg					
	-	±	+	++	+++	Pos.	-	±	+	++	+++	Pos.
(Kidney)	[5]						[5]					
Basophilic tubule	2	3	0	0	0	3	3	2	0	0	0	2
Cellular infiltration, lymphocyte	3	2	0	0	0	2	3	2	0	0	0	2
Cyst, cortex	4	0	1	0	0	1	5	0	0	0	0	0
(Spleen)	[5]						[5]					
Deposit, pigment, brown	0	0	5	0	0	5	0	0	5	0	0	5
Hematopoiesis, extramedullary	0	5	0	0	0	5	1	3	1	0	0	4
(Heart)	[5]						[5]					
No abnormalities												
(Liver)	[5]						[5]					
No abnormalities												
(Adrenal gland)	[5]						[5]					
No abnormalities												
(Stomach)	[5]						[5]					
No abnormalities												
(Ovary)	[5]						[5]					
No abnormalities												

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe; Pos., total of positive grade.

[], number of animals examined.

Table 10-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in males at the end of recovery period

Dose	0 mg/kg						20 mg/kg							
	Grade	-	±	+	++	+++	Pos.	-	±	+	++	+++	Pos.	
(Kidney)	[5]							[5]						
Eosinophilic body, proximal tubule		3	0	2	0	0	2		2	2	1	0	0	3
Basophilic tubule		1	4	0	0	0	4		0	5	0	0	0	5
Cellular infiltration, lymphocyte		0	5	0	0	0	5		0	5	0	0	0	5
(Testis)	[1]													
Atrophy, seminiferous tubule, unilateral		0	0	0	0	1	1							
(Epididymis)	[1]													
Decrease, sperm, unilateral		0	0	0	0	1	1							

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe; Pos., total of positive grade.

[], number of animals examined.

Appendix A

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Content of the test article in the prepared sample

Test article : *N,N,N*-Trimethylmethanaminium hydroxide Date of preparation : Feb. 25. 1999

Lot No. : 81029 Date of determination : Feb. 25. 1999

Carrier : Water for injection

Sample No.	Indicated(A) (mg/mL)	Found(B) (mg/mL)	Mean(C) (mg/mL)	Content B/A × 100 (%)	Mean (%)	B/C × 100 (%)
1	0.500	0.5005	0.5005	100	100	100
2		0.5005		100		100
3		0.5005		100		100
4	1.00	1.007	1.005	101	101	100
5		1.007		101		100
6		1.001		100		99.6
7	2.00	2.014	2.010	101	101	100
8		2.014		101		100
9		2.002		100		99.6

Investigator

Director of Chemical analysis

Appendix B

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

調製検体中の被験物質濃度測定法

被 験 物 質 名 : *N,N,N*-トリメチルメタンアミンヒドロキシド (略称 : TMAH)

分 析 法 : 各濃度の調製検体を一定量ずつ採取し、注射用水を加えて 30 mL とした。
これに指示薬としてプロモクレゾールグリーン・メチルレッド溶液を数滴加えて 0.005 mol/L 塩酸で滴定し、滴定値 (mL) を求めた。注射用水について同様に操作してブランク値 (mL) を求め、滴定値からブランク値を差し引いた値を用いて含量を算出した。

Appendix 1-1
 Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in individual males; the dosage of 0 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Day of recovery	Total frequency			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	period 1~14				
1 (SR)	No abnormality in general condition																																	
2 (SR)	No abnormality in general condition																																	
3 (SR)	No abnormality in general condition																																	
4 (SR)	No abnormality in general condition																																	
5 (SR)	No abnormality in general condition																																	
6 (SD)	No abnormality in general condition																																	
7 (SD)	No abnormality in general condition																																	
8 (SD)	No abnormality in general condition																																	
9 (SD)	No abnormality in general condition																																	
10 (SD)	No abnormality in general condition																																	

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Clinical signs in individual males; the dosage of 5 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Total frequency				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28					
11 (SD)	No abnormality in general condition																																	
12 (SD)	No abnormality in general condition																																	
13 (SD)	No abnormality in general condition																																	
14 (SD)	Salivation occurred just after administration (disappeared within about one hour)																																	1
15 (SD)	No abnormality in general condition																																	

○, observed; —, not observed
 *, the salivation also occurred before administration when the animal was handled.
 SD, scheduled sacrifice at the end of dosing period; SR, scheduled sacrifice at the end of recovery period

Appendix 1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in individual males; the dosage of 10 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Total frequency		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28			
16 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	○	○	-	-	○	○*	○	○*	-	○*	○*	○*	-	○*	○*	○	○	○	○	○	-	○*	16
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	○*	-	-	-	-	-	-	○	-	3
17 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	1
18 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	○	-	2
19 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	-	-	-	○	-	-	-	-	-	-	-	-	2
20 (SD)	Discoloration of eyeball (unilateral)	-	-	-	-	-	-	-	-	-	-	-	-	-	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	17

○, observed; -, not observed

*, the salivation also occurred before administration when the animal was handled.

SD, scheduled sacrifice at the end of dosing period

Appendix 1-1 (continued)
 Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in individual males; the dosage of 20 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Day of recovery period 1~14	Total frequency		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28				
21 (SR)	No abnormality in general condition																																
22 (SR)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○*	
23 (SR)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	○	-	○	○	○	○	-	○	○	-	-	-	○	-	○	-	○	○	○				
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	○	○	-	○	-	○	-	-	-	-	
24 (SR)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	○	-	-	-	-	○	-	○	○	○	○	○	-	○	○	○	○	○*	○*	○*	○*	○*	○*	○*	
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	-	-	-	-	-	-	
25 (SR)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	○	○	○	○	○	○	○*	-	○	-	-	-	-	-	-	-	-	-	○*	-	-	○	-	○*			
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	○	-	○*	○*	○*	○*	○*	○*	○*	○*	○*	-	○	○	-	○*	-	-	-	
26 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	-	-	-	○	-	-	○	-	-	-	-	
27 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	○	○	○	○	○	-	○	○*	-	○	-	○	○	○	○	-	○*	○*	-	○	-	-	-	-	-	-	-	-
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	○	-	○	-	-	-	-	-	-	○*	-	-	○*	-	○*	○	○	○*	○*	
28 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	○	○	-	○	○	○	○	○	-	○	○	○	○	○	○	○	-	○	-	-	-	
	Salivation occurred just after administration (continuously observed for about one hour or more)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	○	-	-	
29 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	-	-	
30 (SD)	No abnormality in general condition																																

○, observed; -, not observed

*, the salivation also occurred before administration when the animal was handled.

SD, scheduled sacrifice at the end of dosing period; SR, scheduled sacrifice at the end of recovery period

Appendix 1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in individual females; the dosage of 0 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Day of recovery period	Total frequency					
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	1~14						
31 (SR)	No abnormality in general condition																																			
32 (SR)	No abnormality in general condition																																			
33 (SR)	No abnormality in general condition																																			
34 (SR)	No abnormality in general condition																																			
35 (SR)	No abnormality in general condition																																			
36 (SD)	No abnormality in general condition																																			
37 (SD)	No abnormality in general condition																																			
38 (SD)	No abnormality in general condition																																			
39 (SD)	No abnormality in general condition																																			
40 (SD)	No abnormality in general condition																																			

Clinical signs in individual females; the dosage of 5 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Total frequency						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28							
41 (SD)	No abnormality in general condition																																			
42 (SD)	No abnormality in general condition																																			
43 (SD)	No abnormality in general condition																																			
44 (SD)	No abnormality in general condition																																			
45 (SD)	No abnormality in general condition																																			

SD, scheduled sacrifice at the end of dosing period; SR, scheduled sacrifice at the end of recovery period

—
5
—

Appendix 1-2 (continued)
 Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Clinical signs in individual females; the dosage of 10 mg/kg

Animal No.	Clinical signs	Day of dosing period																												Total frequency
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
46 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	1
47 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	-	1
48 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	○	-	○	○	○	○	○	○	○	○	-	○	-	○	○	○	○	○	○	○*	17
49 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	○	○	○	-	-	-	-	-	-	-	-	○	-	-	-	4	
50 (SD)	Salivation occurred just after administration (disappeared within about one hour)	-	-	-	-	-	-	-	-	-	-	-	-	-	○	-	○	-	-	-	-	-	-	-	-	-	-	○	-	3

○, observed; -, not observed

*, the salivation also occurred before administration when the animal was handled.

SD, scheduled sacrifice at the end of dosing period

Appendix 2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in individual males; the dosage of 0 mg/kg

Animal No.	Day of dosing period									Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14
1	162.4	193.6	212.0 ^L	238.9 ^L	262.2 ^L	298.5 ^L	317.8 ^L	352.2 ^L	362.7 ^L	370.7	404.4	419.4	447.3	450.7
2	161.3 ^L	197.9	227.2	262.8	292.8	322.5	340.9	364.6	375.5	372.5	393.9	403.3	428.2	436.0
3	168.8	200.7	226.3	260.8	288.4	317.3	347.1	377.6	400.4	397.8 ^H	431.2 ^H	444.6 ^H	473.4 ^H	488.9 ^H
4	162.4	191.9 ^L	212.4	246.3	273.3	306.2	335.6	365.8	375.9	378.7	403.5	415.0	441.8	450.2
5	172.0 ^H	201.3	222.4	252.6	277.4	308.1	325.2	354.4	363.5	362.6 ^L	388.9 ^L	396.5 ^L	421.4 ^L	429.5 ^L
6	169.5	205.3	229.3	266.6	297.5	335.6	357.8	392.4 ^H	406.0					
7	164.0	200.0	225.3	258.6	286.3	316.8	339.1	367.7	375.5					
8	168.3	206.5	234.3	271.2	293.2	324.5	345.9	373.6	385.3					
9	169.7	208.9 ^H	236.8 ^H	275.6 ^H	307.7 ^H	337.8 ^H	362.7 ^H	388.3	407.2 ^H					
10	167.0	205.6	233.0	266.8	289.3	316.0	333.6	354.4	367.2					
N	10	10	10	10	10	10	10	10	10	5	5	5	5	5
Mean	166.5	201.2	225.9	260.0	286.8	318.3	340.6	369.1	381.9	376.5	404.4	415.8	442.4	451.1
S.D.	3.7	5.6	8.4	11.3	13.0	12.4	13.7	14.0	17.0	13.2	16.4	18.5	20.2	23.0
S.E.	1.2	1.8	2.7	3.6	4.1	3.9	4.3	4.4	5.4	5.9	7.3	8.3	9.0	10.3
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A					

Body weight changes in individual males; the dosage of 5 mg/kg

Animal No.	Day of dosing period								
	1	5	8	12	15	19	22	26	28
11	163.6 ^L	196.1	216.9	247.9	272.1	296.1	319.0	344.0	351.3
12	166.1	196.0	216.1 ^L	246.5	272.8	300.6	321.8	348.2	361.1
13	167.5 ^H	204.0 ^H	227.0 ^H	262.8 ^H	288.7 ^H	324.9 ^H	350.5 ^H	382.6 ^H	398.1 ^H
14	165.7	192.5 ^L	218.4	244.8 ^L	263.5 ^L	281.9 ^L	295.5 ^L	314.1 ^L	325.7 ^L
15	165.1	196.8	223.7	253.4	280.4	308.2	328.8	348.6	358.8
N	5	5	5	5	5	5	5	5	5
Mean	165.6	197.1	220.4	251.1	275.5	302.3	323.1	347.5	359.0
S.D.	1.4	4.2	4.7	7.3	9.5	15.8	19.8	24.3	26.0
S.E.	0.6	1.9	2.1	3.3	4.2	7.1	8.8	10.9	11.6
F									
T									
M.C.									

* , significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 T, Student's t-test or Aspin-Welch's t-test Parameter, body weight(g) A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

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Appendix 2-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in individual males; the dosage of 10 mg/kg

Animal No.	Day of dosing period								
	1	5	8	12	15	19	22	26	28
16	167.4	204.0	234.2 ^M	266.0	296.8 ^M	319.2	342.0	360.4	380.9
17	162.8	198.9	226.1	260.7	280.6	300.1	317.3 ^L	341.6 ^L	349.4 ^L
18	168.1 ^M	205.2 ^M	232.2	268.3 ^M	291.1	324.2 ^M	345.0	363.2	376.3
19	166.6	199.1	226.5	260.2	289.6	323.0	347.9 ^M	373.3 ^M	381.7 ^M
20	158.9 ^L	189.6 ^L	214.9 ^L	244.5 ^L	270.0 ^L	299.2 ^L	318.2	348.8	359.7
N	5	5	5	5	5	5	5	5	5
Mean	164.8	199.4	226.8	259.9	285.6	313.1	334.1	357.5	369.6
S.D.	3.9	6.1	7.5	9.3	10.5	12.5	15.1	12.4	14.4
S.E.	1.7	2.7	3.4	4.2	4.7	5.6	6.7	5.6	6.4
F									
T									
M.C.									

Body weight changes in individual males; the dosage of 20 mg/kg

Animal No.	Day of dosing period									Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14
21	174.6 ^M	206.3 ^M	231.5	275.2 ^M	300.8	334.9	358.9	389.5	408.0	404.3	428.6	439.8	465.5	473.2
22	167.5	205.4	233.4 ^M	273.2	304.0 ^M	339.6 ^M	367.5 ^M	399.5 ^M	409.5 ^M	416.8 ^M	442.2 ^M	460.0 ^M	479.4	488.1
23	164.7	191.9	216.8	249.2	270.6	304.7	324.7	347.4	339.9	346.6	383.3	406.6	432.0	442.6
24	165.2	194.9	216.2	244.4	263.3	289.2	302.0	322.7	335.1	339.9 ^L	370.6 ^L	382.2 ^L	410.4 ^L	418.9 ^L
25	168.7	203.8	227.5	263.1	286.0	311.7	335.2	372.6	381.9	383.9	421.8	451.6	484.5 ^M	499.5 ^M
26	165.3	198.9	227.3	260.8	282.7	313.4	330.3	351.9	359.1					
27	158.2 ^L	191.2	219.5	253.4	278.3	313.3	325.1	349.6	354.9					
28	163.9	191.3	214.3	246.7	272.4	305.8	324.1	363.3	367.9					
29	166.3	187.7 ^L	211.7 ^L	237.9 ^L	257.8 ^L	283.7 ^L	300.1 ^L	317.4 ^L	327.5 ^L					
30	163.9	198.6	223.9	258.7	282.3	315.6	335.1	357.2	369.8					
N	10	10	10	10	10	10	10	10	10	5	5	5	5	5
Mean	165.8	197.0	222.2	256.3	279.8	311.2	330.3	357.1	365.4	378.3	409.3	428.0	454.4	464.5
S.D.	4.2	6.6	7.6	12.2	14.8	17.3	21.2	26.0	28.3	34.2	30.8	32.7	32.0	33.2
S.E.	1.3	2.1	2.4	3.9	4.7	5.5	6.7	8.2	9.0	15.3	13.8	14.6	14.3	14.9
F										6.66*	3.54	3.12	2.51	2.08
T										0.11	0.32	0.73	0.71	0.74
M.C.														

*. significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 T, Student's t-test or Aspin-Welch's t-test Parameter, body weight(g) A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in individual females; the dosage of 0 mg/kg

Animal No.	Day of dosing period									Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14
31	137.3	151.4 ^L	160.5	173.2	186.5 ^L	201.3	205.4 ^L	215.3 ^L	225.0	225.3 ^L	238.0 ^L	243.3 ^L	247.3 ^L	252.6 ^L
32	135.2 ^L	155.3	169.4	183.7	194.4	206.9	219.5	236.4 ^L	245.4	241.7	256.2	267.9 ^H	279.9	287.3 ^H
33	140.1	162.4	175.1	187.8	198.6	209.1	227.4	237.7	248.4	250.3 ^H	266.4 ^H	265.6	282.2	287.0
34	143.6	160.6	175.4	189.4	203.1	216.5	222.7	237.5	245.5	240.1	257.6	267.1	282.9 ^H	278.6
35	145.7 ^H	165.5 ^H	179.9 ^H	192.5 ^H	201.1	215.3	215.5	231.5	240.0	246.7	255.6	265.1	281.6	273.1
36	136.2	154.2	167.7	175.6	186.9	204.1	211.9	222.0	233.0					
37	137.8	161.3	166.1	178.0	195.2	203.8	223.7	241.9	233.2					
38	140.3	158.6	171.4	190.8	203.6 ^H	222.9 ^H	233.5 ^H	249.0 ^H	255.0 ^H					
39	139.7	154.9	158.0 ^L	171.8 ^L	189.3	195.1 ^L	208.7	225.1	215.4 ^L					
40	143.8	163.8	179.7	192.2	201.6	216.6	222.5	232.8	238.0					
N	10	10	10	10	10	10	10	10	10	5	5	5	5	5
Mean	140.0	158.8	170.3	183.5	196.1	211.2	219.1	232.9	238.0	240.8	254.8	261.8	274.8	275.7
S.D.	3.5	4.7	7.5	8.2	6.7	8.9	8.7	9.9	11.8	9.6	10.3	10.4	15.4	14.2
S.E.	1.1	1.5	2.4	2.6	2.1	2.8	2.8	3.1	3.7	4.3	4.6	4.7	6.9	6.4
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A					

Body weight changes in individual females; the dosage of 5 mg/kg

Animal No.	Day of dosing period								
	1	5	8	12	15	19	22	26	28
41	149.2 ^H	172.0 ^H	186.3 ^H	204.3 ^H	214.3 ^H	231.5 ^H	251.5 ^H	263.4 ^H	264.4 ^H
42	137.1	157.5 ^H	160.2	171.0	184.3	199.1	205.6	215.7	213.7
43	148.4	168.2 ^H	177.0	194.3	207.8	226.9	234.1	253.9	250.2
44	136.3 ^L	148.2 ^L	152.3 ^L	160.7 ^L	172.9 ^L	182.0 ^L	187.4 ^L	194.9 ^L	197.9 ^L
45	146.7	163.5 ^H	174.8	190.0	198.3	215.3	228.5	242.0	251.6
N	5	5	5	5	5	5	5	5	5
Mean	143.5	161.0	170.1	184.1	195.5	211.0	221.4	234.0	235.6
S.D.	6.4	9.4	13.7	17.8	16.9	20.5	25.1	28.2	28.3
S.E.	2.8	4.2	6.1	8.0	7.6	9.1	11.2	12.6	12.6
M.C.									

*. significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H. highest B. Bartlett's test K. Kruskal-Wallis' H test
 T. Student's t-test or Aspin-Welch's t-test Parameter, body weight(g) A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

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Appendix 2-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Body weight changes in individual females; the dosage of 10 mg/kg

Animal No.	Day of dosing period									
	1	5	8	12	15	19	22	26	28	
46	135.4 ^L	154.3 ^L	163.3 ^L	173.4 ^L	181.7	193.3	194.5 ^L	208.5 ^L	214.5 ^L	
47	143.8	160.6	172.2	180.0	186.2	198.0	204.9	210.9	223.4	
48	138.6	154.5	163.3 ^L	175.8	180.4 ^L	192.4 ^L	205.4	214.2	217.0	
49	142.2	161.8	176.9	190.4	211.1	226.2	235.4	251.4	261.3 ^H	
50	149.4 ^H	170.8 ^H	182.7 ^H	198.4 ^H	214.9 ^H	231.8 ^H	242.7 ^H	254.7 ^H	255.3	
N	5	5	5	5	5	5	5	5	5	
Mean	141.9	160.4	171.7	183.6	194.9	208.3	216.6	227.9	234.3	
S.D.	5.3	6.7	8.5	10.5	16.8	19.1	21.1	23.0	22.2	
S.E.	2.4	3.0	3.8	4.7	7.5	8.5	9.4	10.3	10.0	
F										
T										
M.C.										

Body weight changes in individual females; the dosage of 20 mg/kg

Animal No.	Day of dosing period										Day of recovery period				
	1	5	8	12	15	19	22	26	28	1	5	8	12	14	
51	151.1 ^H	169.6 ^H	181.5	193.5	204.4	221.4	228.7	244.6	255.8	252.2 ^H	266.5 ^H	279.0 ^H	289.2 ^H	288.7 ^H	
52	132.2 ^L	144.3 ^L	153.6 ^L	157.7 ^L	169.2 ^L	175.5 ^L	184.6 ^L	193.4 ^L	192.1 ^L	192.6 ^L	199.9 ^L	200.5 ^L	210.1 ^L	211.1 ^L	
53	134.4	151.6	164.1	176.9	185.4	198.2	204.1	213.8	213.5	215.2	223.9	232.4	241.1	243.1	
54	140.7	159.6	169.7	183.2	195.6	212.5	217.7	224.5	236.2	237.0	243.3	256.1	267.3	266.1	
55	136.9	156.4	171.1	183.3	193.1	207.2	208.9	221.8	220.1	218.5	221.7	232.0	235.7	241.4	
56	143.3	157.8	162.5	175.3	175.8	191.6	196.3	207.9	211.3						
57	139.0	157.6	166.8	179.1	187.2	200.1	207.7	217.0	221.1						
58	142.1	165.2	175.0	185.3	192.3	200.2	205.2	213.9	223.4						
59	149.2	169.4	182.8 ^H	199.9 ^H	210.1 ^H	226.4 ^H	232.8 ^H	251.4 ^H	257.5 ^H						
60	140.7	158.1	171.0	188.3	200.4	218.8	226.8	241.2	246.3						
N	10	10	10	10	10	10	10	10	10	5	5	5	5	5	
Mean	141.0	159.0	169.8	182.3	191.4	205.2	211.3	223.0	227.7	223.1	231.1	240.5	248.7	250.1	
S.D.	5.9	7.8	8.8	11.4	12.5	15.4	15.2	18.0	21.0	22.7	25.1	29.4	30.4	29.1	
S.E.	1.9	2.5	2.8	3.6	4.0	4.9	4.8	5.7	6.6	10.1	11.2	13.2	13.6	13.0	
F										5.60	5.89	8.00*	3.90	4.18	
T										1.61	1.95	1.56	1.71	1.77	
M.C.															

*. significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H. highest B. Bartlett's test K. Kruskal-Wallis' H test
 T. Student's t-test or Aspin-Welch's t-test Parameter, body weight(g) A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

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Appendix 3-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in individual males; the dosage of 0 mg/kg

Animal No.	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
1	21.8	22.7 ^L	22.4 ^L	27.5 ^L	30.2	31.7
2	21.2 ^L	25.2	26.6	27.5 ^L	29.7	27.5 ^L
3	25.7	25.5	25.8	29.1	32.9	29.0
4	23.1	27.8	29.4	33.0	33.6 ^H	32.8 ^H
5	27.6 ^H	27.5	25.9	31.3	29.1 ^L	30.7
6	23.8	25.6	31.0 ^H	32.9		
7	22.0	25.4	27.5	29.0		
8	24.8	26.0	27.0	31.4		
9	25.3	29.9 ^H	28.8	33.3 ^H		
10	24.9	26.5	28.8	31.1		
N	10	10	10	10	5	5
Mean	24.0	26.2	27.3	30.6	31.1	30.3
S.D.	2.0	1.9	2.4	2.2	2.0	2.1
S.E.	0.6	0.6	0.8	0.7	0.9	0.9
M.C.	B->A->D	B->A	B->K	B->A		

Food consumption in individual males; the dosage of 5 mg/kg

Animal No.	Day of dosing period			
	1	8	15	22
11	22.8	22.8	26.4	27.2 ^L
12	21.6 ^L	22.6 ^L	26.1	27.4
13	22.9	25.7	30.0 ^H	34.2 ^H
14	23.6 ^H	27.2 ^H	26.9	27.6
15	23.4	24.7	25.9 ^L	29.8
N	5	5	5	5
Mean	22.9	24.6	27.1	29.2
S.D.	0.8	2.0	1.7	3.0
S.E.	0.3	0.9	0.8	1.3
M.C.	1.20	-----	-----	-----

*. significantly different from control. p<0.05 L, lowest M.C., multiple comparisons
 **. significantly different from control. p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 T, Student's t-test or Aspin-Welch's t-test Parameter, food consumption(g) A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 3-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in individual males; the dosage of 10 mg/kg

Animal No.	Day of dosing period			
	1	8	15	22
16	22.2	25.0	29.8	28.4
17	19.8	25.5	26.4 ^L	28.2 ^L
18	22.4 ^H	27.7 ^H	30.3 ^H	31.7 ^H
19	21.0	23.1	28.0	30.8
20	19.5 ^L	23.0 ^L	26.9	29.5
N	5	5	5	5
Mean	21.0	24.9	28.3	29.7
S.D.	1.3	1.9	1.7	1.5
S.E.	0.6	0.9	0.8	0.7
F				
T				
M.C.	3.14*	-----	-----	-----

Food consumption in individual males; the dosage of 20 mg/kg

Animal No.	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
21	20.7	28.0 ^H	28.3	31.8	39.1	33.6
22	20.4	26.3	27.6	33.5	40.9 ^H	34.1
23	15.4 ^L	23.3	44.5 ^H	31.3	38.2 ^H	30.0
24	20.3	23.2	25.5	24.3 ^L	38.4 ^L	30.0 ^L
25	20.0	25.6	29.0	30.7	38.5	39.8 ^H
26	19.0	24.8	25.0	27.9		
27	16.0	24.4	25.5	26.5		
28	18.7	21.8 ^L	26.3	30.0		
29	17.7	21.5 ^L	23.1 ^L	24.7		
30	21.2 ^H	25.2	29.6	34.3 ^H		
N	10	10	10	10	5	5
Mean	19.1	24.6	28.6	29.6	37.0	34.0
S.D.	2.0	1.9	5.0	3.6	4.9	3.1
S.E.	0.6	0.6	1.9	1.1	2.2	1.7
F					5.9	3.2
T					2.48*	2.12
M.C.	6.23**	-----	-----	-----		

*, significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 T, Student's t-test or Aspin-Welch's t-test Parameter, food consumption(g) A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 3-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in individual females; the dosage of 0 mg/kg

Animal No.	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
31	15.1 ^L	20.7 ^H	18.3	21.0	16.4 ^L	22.3 ^L
32	18.1	19.2	21.5 ^H	25.2	24.3 ^H	24.4
33	20.3 ^H	19.5	20.5 ^H	24.1	22.0	26.6 ^H
34	18.8	17.5	18.6	24.2	22.5	25.2
35	18.7	16.1	21.0	21.2	21.4	25.5
36	18.8	16.0 ^L	19.7	20.9 ^L		
37	20.1	17.6	18.6	26.6 ^H		
38	18.4	18.6	20.6	24.9		
39	18.5	16.6	15.5 ^L	24.5		
40	19.7	18.5	19.7	24.2		
N	10	10	10	10	5	5
Mean	18.7	18.0	19.4	23.7	21.3	24.8
S.D.	1.5	1.5	1.7	2.0	3.0	1.6
S.E.	0.5	0.5	0.6	0.6	1.3	0.7
M.C.	B->A->D	B->A	B->A	B->A		

Food consumption in individual females; the dosage of 5 mg/kg

Animal No.	Day of dosing period			
	1	8	15	22
41	20.5 ^H	19.7 ^H	22.5 ^H	21.2
42	16.3 ^L	17.8 ^L	16.8	18.5 ^L
43	20.0	19.4	20.9	26.2 ^H
44	18.1	17.8 ^L	16.3 ^L	19.0
45	18.1	18.9	21.2	21.5
N	5	5	5	5
Mean	18.6	18.7	19.5	21.3
S.D.	1.7	0.9	2.8	3.0
S.E.	0.8	0.4	1.3	1.4
M.C.	0.06	-----	-----	-----

*, significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 T, Student's t-test or Aspin-Welch's t-test Parameter, food consumption(g) A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

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Appendix 3-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Food consumption in individual females; the dosage of 10 mg/kg

Animal No.	Day of dosing period			
	1	8	15	22
46	15.7 ^L	15.8 ^L	18.2 ^L	18.5 ^L
47	18.5	19.1	20.0	19.0
48	16.0	17.5	18.6	19.2
49	19.1	18.6	21.8	23.9
50	21.9 ^H	21.9 ^H	22.5 ^H	26.7 ^H
N	5	5	5	5
Mean	18.2	18.6	20.2	21.0
S.D.	2.5	2.2	1.9	3.7
S.E.	1.1	1.0	0.8	1.6
F				
T				
M.C.	0.46	-----	-----	-----

Food consumption in individual females; the dosage of 20 mg/kg

Animal No.	Day of dosing period				Day of recovery period	
	1	8	15	22	1	8
51	17.1	21.1	22.8	21.9	22.1	28.3 ^H
52	16.4	16.4	14.7 ^L	18.8 ^L	19.2 ^L	18.3
53	14.5 ^L	16.1 ^L	17.5	19.7	23.1 ^H	17.2
54	14.6	18.0	22.2	23.1	22.3	26.5
55	16.3	17.1	20.2	20.9	23.0	16.4 ^L
56	15.4	17.3	15.6	21.4		
57	17.3	19.1	21.2	19.9		
58	17.8 ^H	19.2	20.9	22.3		
59	17.3	21.3 ^H	23.3 ^H	25.2 ^H		
60	14.8	19.6	19.9	21.1		
N	10	10	10	10	5	5
Mean	16.2	18.5	19.8	21.4	21.9	21.3
S.D.	1.2	1.8	3.0	1.8	1.6	5.6
S.E.	0.4	0.6	0.9	0.6	0.7	2.5
F					3.45	12.22 [*]
T					0.41	1.33
M.C.	3.41 ^{**}	-----	-----	-----		

*. significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H, highest B. Bartlett's test K. Kruskal-Wallis' H test
 T. Student's t-test or Aspin-Welch's t-test Parameter, food consumption(g) A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

Appendix 4-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual males on day 26 of dosing period

Dose (mg/kg)	Animal No.	Color ^{a)}	Turbidity ^{b)}	pH	Protein ^{c)}	Glucose ^{d)}	Ketone ^{b)}	Bilirubin ^{b)}	Occult blood ^{b)}	Urobilinogen ^{e)}
0	1	ly	-	8.5	+	-	-	-	-	±
	2	ly	-	7.0	+	-	±	-	-	±
	3	ly	-	7.0	+	-	±	-	-	±
	4	ly	-	7.5	+	-	-	-	-	±
	5	ly	-	≈9.0	+	-	±	-	-	±
	6	ly	-	7.5	±	-	-	-	-	±
	7	ly	-	7.5	+	-	±	-	-	±
	8	ly	-	7.5	+	-	+	-	-	±
	9	ly	-	8.0	+	-	-	-	-	±
	10	ly	-	7.0	±	-	±	-	-	±
5	11	ly	-	7.0	+	-	±	-	-	±
	12	ly	-	8.0	±	-	-	-	-	±
	13	ly	-	8.5	+	-	±	-	-	±
	14	ly	-	8.0	+	-	±	-	-	±
	15	ly	-	7.5	+	-	±	-	-	±
10	16	ly	-	8.5	+	-	+	-	-	±
	17	ly	-	7.5	±	-	-	-	-	±
	18	ly	-	8.0	±	-	±	-	-	±
	19	ly	-	8.0	+	-	±	-	+	±
	20	ly	-	7.5	+	-	±	-	-	±
20	21	ly	-	7.5	+	-	±	-	-	±
	22	ly	-	7.0	+	-	±	-	-	±
	23	ly	-	7.0	+	-	±	-	-	±
	24	ly	-	≈9.0	+	-	±	-	-	±
	25	ly	-	≈9.0	+	-	-	-	-	±
	26	ly	-	7.5	+	-	±	-	-	±
	27	ly	-	7.0	+	-	+	-	-	±
	28	ly	-	8.5	+	-	-	-	-	±
	29	ly	-	7.5	+	-	+	-	-	±
	30	ly	-	≈9.0	+	-	±	-	-	±

a) ly, light yellow

b) -, negative; ±, trace; +, slight

c) -, negative; ±, trace; +, 30 mg/dL

d) -, negative

e) ±, 0.1 E.U./dL; +, 1.0 E.U./dL

Appendix 4-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual males on day 26 of dosing period

Dose (mg/kg)	Animal No.	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
				Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
0	1	45.3	1.017	47.2	62.6	37.3	2.14	2.84	1.69	0.75
	2	19.4	1.043	92.5	199.0	124.5	1.79	3.86	2.42	0.46
	3	26.7	1.037	79.7	177.4	103.0	2.13	4.74	2.75	0.45
	4	33.8	1.029	63.0	137.3	72.2	2.13	4.64	2.44	0.46
	5	19.3	1.047	105.6	227.0	137.2	2.04	4.38	2.65	0.47
	6	45.5	1.025	47.9	117.2	60.8	2.18	5.33	2.77	0.41
	7	19.6	1.048	109.3	223.5	134.0	2.14	4.38	2.63	0.49
	8	16.0	1.047	110.7	225.9	138.9	1.77	3.61	2.22	0.49
	9	23.9	1.045	88.9	196.9	108.6	2.12	4.71	2.60	0.45
	10	19.7	1.039	77.6	194.4	98.7	1.53	3.83	1.94	0.40
	Mean	26.9	1.038	82.2	176.1	101.5	2.00	4.23	2.41	0.48
	S. D.	10.9	0.011	23.7	54.2	34.9	0.22	0.71	0.36	0.10
	M. C.	B→K	B→A	B→A	B→A	B→A	B→A	B→A	B→A	B→A
5	11	29.2	1.022	36.4	109.6	47.9	1.06	3.20	1.40	0.33
	12	24.3	1.035	85.1	184.2	106.8	2.07	4.48	2.60	0.46
	13	30.1	1.034	82.1	185.3	103.8	2.47	5.58	3.12	0.44
	14	21.0	1.033	57.4	179.8	83.9	1.21	3.78	1.76	0.32
	15	20.1	1.042	95.3	212.6	114.8	1.92	4.27	2.31	0.45
	Mean	24.9	1.033	71.3	174.3	91.4	1.75	4.26	2.24	0.40
	S. D.	4.6	0.007	23.9	38.4	26.9	0.60	0.89	0.68	0.07
	M. C.	---	---	---	---	---	---	---	---	---
10	16	23.1	1.036	74.3	178.2	85.9	1.72	4.12	1.98	0.42
	17	30.7	1.022	38.4	117.4	54.7	1.18	3.60	1.68	0.33
	18	28.6	1.029	67.3	149.3	86.1	1.92	4.27	2.46	0.45
	19	26.0	1.033	62.6	172.2	94.0	1.63	4.48	2.44	0.36
	20	27.3	1.029	61.2	153.8	88.6	1.67	4.20	2.42	0.40
	Mean	27.1	1.030	60.8	154.2	81.9	1.62	4.13	2.20	0.39
	S. D.	2.8	0.005	13.5	23.9	15.5	0.27	0.33	0.35	0.05
	M. C.	---	---	---	---	---	---	---	---	---
20	21	23.2	1.040	98.2	211.9	129.5	2.28	4.92	3.00	0.46
	22	25.7	1.033	71.1	169.1	90.5	1.83	4.35	2.33	0.42
	23	25.1	1.021	50.3	116.5	77.9	1.26	2.92	1.96	0.43
	24	18.4	1.039	98.6	191.3	117.6	1.81	3.52	2.16	0.52
	25	28.0	1.030	76.8	157.6	103.7	2.15	4.41	2.90	0.49
	26	29.3	1.030	77.0	158.8	106.8	2.26	4.65	3.13	0.48
	27	18.7	1.034	65.2	186.2	95.4	1.22	3.48	1.78	0.35
	28	25.9	1.031	70.7	174.3	95.6	1.83	4.51	2.48	0.41
	29	14.4	1.043	100.9	220.3	144.0	1.45	3.17	2.07	0.46
	30	30.8	1.024	52.7	151.4	82.8	1.62	4.66	2.55	0.35
	Mean	24.0	1.033	76.2	173.7	104.4	1.77	4.06	2.44	0.44
	S. D.	5.3	0.007	18.2	30.5	20.8	0.39	0.71	0.46	0.06
	M. C.	---	---	---	---	---	---	---	---	---

M.C., multiple comparisons B, Bartlett's test K, Kruskal-Wallis' H test A, Analysis of variance

Appendix 4-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual females on day 26 of dosing period

Dose (mg/kg)	Animal No.	Color ^{a)}	Turbidity ^{b)}	pH	Protein ^{c)}	Glucose ^{d)}	Ketone ^{b)}	Bilirubin ^{b)}	Occult blood ^{b)}	Urobili- nogen ^{e)}
0	31	ly	—	7.0	—	—	—	—	—	±
	32	ly	—	7.5	—	—	—	—	—	±
	33	ly	—	7.0	—	—	—	—	—	±
	34	ly	—	7.0	—	—	—	—	—	±
	35	ly	—	6.5	±	—	—	—	—	±
	36	ly	—	7.0	±	—	—	—	—	±
	37	ly	—	7.0	—	—	—	—	—	±
	38	ly	—	7.5	±	—	—	—	—	±
	39	ly	—	7.0	±	—	—	—	—	±
	40	ly	—	7.5	±	—	—	±	—	+
5	41	ly	—	7.0	—	—	—	—	—	±
	42	ly	—	7.0	—	—	—	—	—	±
	43	ly	—	8.5	—	—	—	—	—	±
	44	ly	—	9.0	—	—	—	—	—	±
	45	ly	—	7.5	—	—	—	—	—	±
10	46	ly	—	7.5	—	—	—	—	—	±
	47	ly	—	7.5	—	—	—	—	—	±
	48	ly	—	7.0	—	—	—	—	—	±
	49	ly	—	8.0	—	—	—	—	—	±
	50	ly	—	7.5	—	—	—	—	—	±
20	51	ly	—	7.5	—	—	—	—	—	±
	52	ly	—	7.0	—	—	—	—	—	±
	53	ly	—	7.0	—	—	—	—	—	±
	54	ly	—	7.5	—	—	—	—	—	±
	55	ly	—	7.5	—	—	—	—	—	±
	56	ly	—	8.0	—	—	—	—	—	±
	57	ly	—	6.5	—	—	±	—	—	+
	58	ly	—	6.5	—	—	—	—	—	+
	59	ly	—	7.5	—	—	—	—	—	±
	60	ly	—	8.0	—	—	—	—	—	±

a) ly, light yellow

b) —, negative; ±, trace

c) —, negative; ±, trace

d) —, negative

e) ±, 0.1 E. U./dL; +, 1.0 E. U./dL

Appendix 4-1-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual females on day 26 of dosing period

Dose (mg/kg)	Animal No.	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
				Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
0	31	17.5	1.029	80.2	182.6	97.6	1.40	3.20	1.71	0.44
	32	24.1	1.027	71.6	166.8	93.2	1.73	4.02	2.25	0.43
	33	13.0	1.033	58.6	170.9	83.4	0.76	2.22	1.08	0.34
	34	13.6	1.030	46.6	161.4	52.3	0.63	2.20	0.71	0.29
	35	10.8	1.052	93.2	271.3	137.2	1.01	2.93	1.48	0.34
	36	11.1	1.043	102.5	232.1	116.8	1.14	2.58	1.30	0.44
	37	9.1	1.033	75.9	153.3	67.3	0.69	1.40	0.61	0.50
	38	21.0	1.031	80.1	193.0	95.6	1.68	4.05	2.01	0.42
	39	12.7	1.047	132.7	253.9	135.1	1.69	3.22	1.72	0.52
	40	16.0	1.035	90.7	216.6	121.3	1.45	3.47	1.94	0.42
		Mean	14.9	1.036	83.2	200.2	100.0	1.22	2.93	1.48
	S. D.	4.8	0.008	23.9	41.2	28.0	0.43	0.84	0.55	0.07
	M. C.	B→A	B→A	B→A	B→A	B→K	B→A	B→A	B→A	B→A
5	41	17.7	1.036	100.7	201.4	107.9	1.78	3.56	1.91	0.50
	42	14.4	1.038	92.6	205.6	118.8	1.33	2.96	1.71	0.45
	43	24.0	1.012	26.9	66.1	21.3	0.65	1.59	0.51	0.41
	44	13.0	1.042	80.4	216.8	106.2	1.05	2.82	1.38	0.37
	45	18.4	1.032	80.8	174.5	89.8	1.49	3.21	1.65	0.46
		Mean	17.5	1.032	76.3	172.9	88.8	1.26	2.83	1.43
	S. D.	4.3	0.012	28.9	61.7	39.1	0.43	0.75	0.55	0.05
	M. C.	----	----	----	----	----	----	----	----	----
10	46	10.8	1.041	54.3	204.3	101.8	0.59	2.21	1.10	0.27
	47	19.7	1.030	68.0	160.6	95.0	1.34	3.16	1.87	0.42
	48	18.5	1.031	86.6	170.6	91.2	1.60	3.16	1.69	0.51
	49	21.4	1.032	79.8	177.5	102.0	1.71	3.80	2.18	0.45
	50	18.2	1.035	92.3	191.9	101.1	1.68	3.49	1.84	0.48
	Mean	17.7	1.034	76.2	181.0	98.2	1.38	3.16	1.74	0.43
	S. D.	4.1	0.004	15.2	17.3	4.9	0.47	0.60	0.40	0.09
	M. C.	----	----	----	----	----	----	----	----	----
20	51	31.9	1.021	57.5	133.3	78.0	1.83	4.25	2.49	0.43
	52	20.9	1.015	25.1	78.4	26.4	0.52	1.64	0.55	0.32
	53	19.2	1.026	46.9	133.8	63.7	0.90	2.57	1.22	0.35
	54	17.4	1.039	81.0	201.2	112.3	1.41	3.50	1.95	0.40
	55	22.4	1.024	37.9	128.3	61.5	0.85	2.87	1.38	0.30
	56	11.0	1.049	87.3	250.9	123.8	0.96	2.76	1.36	0.35
	57	16.8	1.035	64.4	160.6	94.5	1.08	2.70	1.59	0.40
	58	13.7	1.044	86.5	209.7	118.7	1.19	2.87	1.63	0.41
	59	21.1	1.034	79.5	183.0	109.1	1.68	3.86	2.30	0.43
	60	21.9	1.027	69.5	149.5	95.4	1.52	3.27	2.09	0.46
		Mean	19.6	1.031	63.6	162.9	88.3	1.19	3.03	1.66
	S. D.	5.7	0.011	21.4	49.5	30.8	0.41	0.73	0.57	0.05
	M. C.	----	----	----	----	----	----	----	----	----

M.C., multiple comparisons

B. Bartlett's test

K, Kruskal-Wallis' H test

A, analysis of variance

Appendix 4-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual males on day 12 of recovery period

Dose (mg/kg)	Animal No.	Color ^{a)}	Turbidity ^{b)}	pH	Protein ^{c)}	Glucose ^{d)}	Ketone ^{b)}	Bilirubin ^{b)}	Occult blood ^{b)}	Urobili- nogen ^{e)}
0	1	ly	—	8.0	+	—	±	—	—	±
	2	ly	—	7.5	+	—	+	—	—	±
	3	ly	—	7.5	—	—	±	—	—	±
	4	ly	—	8.0	±	—	—	—	—	±
	5	ly	—	8.5	+	—	±	—	—	±
20	21	ly	—	8.5	+	—	±	—	—	±
	22	ly	—	8.5	+	—	±	—	—	±
	23	ly	—	8.0	—	—	—	—	—	±
	24	ly	—	8.0	+	—	±	—	—	±
	25	ly	—	7.5	+	—	+	—	—	+

a) ly, light yellow

b) —, negative; ±, trace; +, slight

c) —, negative; ±, trace; +, 30 mg/dL

d) —, negative

e) ±, 0.1 E.U./dL; +, 1.0 E.U./dL

Appendix 4-2-1(continued)
 Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual males on day 12 of recovery period

Dose (mg/kg)	Animal No.	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
				Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
0	1	35.7	1.026	55.5	100.8	50.3	1.98	3.60	1.80	0.55
	2	23.9	1.041	90.1	169.7	106.4	2.15	4.06	2.54	0.53
	3	46.1	1.023	55.9	106.0	64.2	2.58	4.89	2.96	0.53
	4	39.2	1.027	59.3	120.7	62.5	2.32	4.73	2.45	0.49
	5	19.4	1.046	118.5	212.2	130.7	2.30	4.12	2.54	0.56
	Mean	32.9	1.033	75.9	141.9	82.8	2.27	4.28	2.46	0.53
S. D.	11.0	0.010	27.9	47.8	34.2	0.22	0.53	0.42	0.03	
20	21	22.4	1.052	136.0	228.7	146.1	3.05	5.12	3.27	0.59
	22	32.4	1.032	78.7	156.1	95.2	2.55	5.06	3.08	0.50
	23	25.3	1.038	107.2	182.9	111.5	2.71	4.63	2.82	0.59
	24	26.9	1.036	89.3	176.9	107.1	2.40	4.76	2.88	0.50
	25	25.9	1.043	106.0	198.7	121.1	2.75	5.15	3.14	0.53
	Mean	26.6	1.040	103.4	188.7	116.2	2.69	4.94	3.04	0.54
S. D.	3.7	0.008	21.8	27.1	19.1	0.24	0.23	0.19	0.05	
F	9.1*	1.762	1.6	3.1	3.2	1.20	5.07	5.04	2.87	
T	1.2	1.329	1.7	1.9	1.9	2.89*	2.57*	2.84*	0.42	

*. significantly different from control. $p < 0.05$
 T. Student's t-test or Aspin-welch's t-test

Appendix 4-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual females on day 12 of recovery period

Dose (mg/kg)	Animal No.	Color ^{a)}	Turbidity ^{b)}	pH	Protein ^{c)}	Glucose ^{d)}	Ketone ^{b)}	Bilirubin ^{b)}	Occult blood ^{b)}	Urobili- nogen ^{e)}
0	31	ly	—	≥9.0	—	—	—	—	—	±
	32	ly	—	7.0	—	—	—	—	—	±
	33	ly	—	7.0	—	—	—	—	—	±
	34	ly	—	8.5	±	—	—	—	—	±
	35	ly	—	7.0	—	—	—	—	—	±
20	51	ly	—	7.5	—	—	—	—	—	±
	52	ly	—	6.5	—	—	±	—	—	±
	53	ly	—	7.5	±	—	—	—	—	+
	54	ly	—	7.5	—	—	—	—	—	±
	55	ly	—	7.0	—	—	—	—	—	±

a) ly, light yellow

b) —, negative; ±, trace

c) —, negative; ±, trace

d) —, negative

e) ±, 0.1 E. U./dL; +, 1.0 E. U./dL

Appendix 4-2-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Urinalysis in individual females on day 12 of recovery period

Dose (mg/kg)	Animal No.	Volume (mL/24hr)	Specific gravity	Concentration			Excretion			Na/K
				Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/24hr)	K (mEq/24hr)	Cl (mEq/24hr)	
0	31	15.5	1.038	102.0	186.3	101.7	1.58	2.89	1.58	0.55
	32	18.3	1.036	108.6	181.1	111.2	1.99	3.31	2.03	0.60
	33	19.1	1.032	95.0	172.2	97.6	1.81	3.29	1.86	0.55
	34	16.0	1.044	115.2	213.2	125.2	1.84	3.41	2.00	0.54
	35	19.6	1.037	117.3	186.0	124.5	2.30	3.65	2.44	0.63
	Mean	17.7	1.037	107.6	187.8	112.0	1.90	3.31	1.98	0.57
S.D.	1.8	0.004	9.3	15.3	12.7	0.27	0.27	0.31	0.04	
20	51	24.9	1.028	85.8	159.6	93.0	2.14	3.97	2.32	0.54
	52	15.7	1.034	98.2	178.7	105.1	1.54	2.81	1.65	0.55
	53	10.5	1.042	130.0	216.5	121.6	1.37	2.27	1.28	0.60
	54	24.1	1.032	96.1	172.4	112.5	2.32	4.15	2.71	0.56
	55	16.4	1.032	96.9	157.7	87.7	1.59	2.59	1.44	0.61
	Mean	18.3	1.034	101.4	177.0	104.0	1.79	3.16	1.88	0.57
S.D.	6.1	0.005	16.7	23.8	13.9	0.41	0.85	0.61	0.03	
F	10.9*	1.426	3.3	2.4	1.2	2.42	9.51*	3.83	1.58	
T	0.2	1.258	0.7	0.9	1.0	0.51	0.38	0.33	0.09	

*, significantly different from control, $p < 0.05$

T. Student's t-test or Aspin-welch's t-test

Appendix 5-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of dosing period; the dosage of 0 mg/kg

Animal No.	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
1 (R.T.)										
2 (R.T.)										
3 (R.T.)										
4 (R.T.)										
5 (R.T.)										
6	718	14.9	43.0	59.9	20.8	34.7 ^H	4.3 ^H	110.2	19.2	19.6 ^L
7	688 ^L	14.8	42.9	62.4 ^H	21.5 ^H	34.5	3.7	97.1 ^L	21.5 ^H	21.3
8	689	14.0 ^L	41.1 ^L	59.6	20.3	34.1	3.2 ^L	112.0 ^H	16.9	22.2
9	723	14.8	42.7	59.0 ^L	20.5	34.7 ^H	3.9	97.6	16.8 ^L	19.7
10	766 ^H	15.1 ^H	45.2 ^H	59.0 ^L	19.7 ^L	33.4 ^L	3.3	101.8	19.3	22.5 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	717	14.7	43.0	60.0	20.6	34.3	3.7	103.7	18.7	21.1
S.D.	32	0.4	1.5	1.4	0.7	0.5	0.4	7.0	2.0	1.4
S.E.	14	0.2	0.7	0.6	0.3	0.2	0.2	3.1	0.9	0.6
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->K	B->A	B->A->D	B->A

Animal No.	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
1 (R.T.)							
2 (R.T.)							
3 (R.T.)							
4 (R.T.)							
5 (R.T.)							
6	95	0	8	0 ^L	0	0 ^L	92 ^H
7	97 ^H	0	7 ^L	0 ^L	0	1	92 ^H
8	76	0	13	0 ^L	0	8 ^H	79
9	66	0	26 ^H	2	0	1	71 ^L
10	40 ^L	0	19	4 ^H	0	6	71 ^L
N	5	5	5	5	5	5	5
Mean	75	0	15	1	0	3	81
S.D.	23	0	8	2	0	4	11
S.E.	10	0	4	1	0	2	5
M.C.	B->A		B->A	B->A	K	B->A	B->A

*. significantly different from control. $p < 0.05$ L, lowest M.C., multiple comparisons
 **. significantly different from control. $p < 0.01$ H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 5-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of dosing period; the dosage of 5 mg/kg

Animal No.	R B C ($\times 10^6/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
11	692	14.5	43.3	62.6 ^H	21.0	33.5 ^L	3.0 ^L	96.9	16.1 ^L	18.6 ^L
12	681	14.9	42.1	61.8	21.9 ^H	35.4 ^H	3.3	99.6 ^H	19.5	19.4
13	668 ^L	14.3 ^L	41.0 ^L	61.4	21.4	34.9	3.5 ^H	97.6	19.5	21.3
14	725	15.0	42.9	59.2 ^L	20.7 ^L	35.0	3.4	86.1 ^L	24.1 ^H	22.2
15	732 ^H	15.5 ^H	45.2 ^H	61.8	21.2	34.3	3.0 ^L	95.4	22.0	23.5 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	700	14.8	42.9	61.4	21.2	34.6	3.2	95.1	20.2	21.0
S.D.	28	0.5	1.6	1.3	0.5	0.7	0.2	5.3	3.0	2.0
S.E.	12	0.2	0.7	0.6	0.2	0.3	0.1	2.4	1.3	0.9
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	1.10	-----

Animal No.	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
11	96	0	2 ^L	1	0 ^L	2	95 ^H
12	97 ^H	0	2 ^L	2 ^H	1 ^H	3	92
13	64 ^L	0	10	0 ^L	0 ^L	4 ^H	86
14	71	0	6	0 ^L	0 ^L	0 ^L	94
15	78	0	12 ^H	1	0 ^L	3	84 ^L
N	5	5	5	5	5	5	5
Mean	81	0	6	1	0	2	90
S.D.	15	0	5	1	0	2	5
S.E.	7	0	2	0	0	1	2
M.C.	-----	-----	-----	-----	-----	-----	-----

*. significantly different from control. $P < 0.05$
 **. significantly different from control. $P < 0.01$
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons

B. Bartlett's test

A. analysis of variance

K. Kruskal-Wallis' H test

D. Dunnett's test or Dunnett type mean rank test

Appendix 5-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of dosing period; the dosage of 10 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μ m ³)	M C H (Pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
16	653 ^L	14.1 ^L	39.8 ^L	61.0 ^M	21.6 ^M	35.4 ^M	5.8 ^M	108.2	16.4	20.6
17	747 ^M	15.6 ^M	44.9 ^M	60.1	20.9	34.7	1.5 ^L	103.2	16.8	19.8
18	716	14.7	43.2	60.4	20.5 ^L	34.0 ^L	2.9	93.1 ^L	20.0 ^M	21.5 ^M
19	700	14.6	41.9	59.9 ^L	20.9	34.8	3.6	96.0	18.4	20.8
20	684	14.4	41.7	61.0 ^M	21.1	34.5	2.9	110.2 ^M	14.7 ^L	19.1 ^L
N	5	5	5	5	5	5	5	5	5	5
Mean	700	14.7	42.3	60.5	21.0	34.7	3.3	102.1	17.3	20.4
S.D.	35	0.6	1.9	0.5	0.4	0.5	1.6	7.5	2.0	0.9
S.E.	16	0.3	0.8	0.2	0.2	0.2	0.7	3.3	0.9	0.4
M.C.									1.09	

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
16	96	0	7	1 ^L	0	2	90
17	64	0	4	0 ^L	0	0 ^L	96 ^M
18	119 ^M	0	3 ^L	2	0	2	93
19	57	0	8	1	0	4 ^M	87
20	42 ^L	0	14 ^M	3 ^M	0	4 ^M	79 ^L
N	5	5	5	5	5	5	5
Mean	76	0	7	1	0	2	89
S.D.	31	0	4	1	0	2	7
S.E.	14	0	2	1	0	1	3
M.C.							

*, significantly different from control, P<0.05
 **, significantly different from control, P<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 5-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of dosing period; the dosage of 20 mg/kg

Animal No.	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
21 (R.T.)										
22 (R.T.)										
23 (R.T.)										
24 (R.T.)										
25 (R.T.)										
26	762 ^H	16.0 ^H	45.0 ^H	59.1 ^L	21.0 ^L	35.6	3.6	99.6	13.5	16.0 ^L
27	689	15.0	41.8	60.6	21.8 ^H	35.9 ^H	4.2 ^H	104.0	13.1 ^L	17.1
28	673	14.5	41.9	62.3 ^H	21.5	34.6	3.6	96.7 ^L	13.5	17.9
29	719	15.1	43.9	61.0	21.0 ^L	34.4 ^L	2.1 ^L	99.6	16.1 ^H	20.0
30	662 ^L	14.4 ^L	40.5 ^L	61.2	21.8 ^H	35.6	2.8	110.4 ^H	14.6	20.9 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	701	15.0	42.6	60.8	21.4	35.2	3.3	102.1	14.2	18.4
S.D.	40	0.6	1.8	1.2	0.4	0.7	0.8	5.3	1.2	2.0
S.E.	18	0.3	0.8	0.5	0.2	0.3	0.4	2.4	0.5	0.9
M.C.									3.37*	

Animal No.	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
21 (R.T.)							
22 (R.T.)							
23 (R.T.)							
24 (R.T.)							
25 (R.T.)							
26	82	0	4 ^L	1 ^H	0	3 ^H	92
27	96 ^H	0	0	0 ^L	0	4 ^H	90
28	59	0	0	0 ^L	0	1 ^L	94 ^H
29	92	0	0	0 ^L	0	1 ^L	94 ^H
30	54 ^L	0	15 ^H	1 ^H	0	2 ^L	82 ^L
N	5	5	5	5	5	5	5
Mean	77	0	3	0	0	2	90
S.D.	20	0	2	1	0	1	2
S.E.	9	0	2	0	0	0	2
M.C.							

*, significantly different from control, $P < 0.05$
 **, significantly different from control, $P < 0.01$
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test

A, analysis of variance

K, Kruskal-Wallis' H test

D, Dunnett's test or Dunnett type mean rank test

Appendix 5-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of dosing period; the dosage of 0 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (fL)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
31 (R.T.)										
32 (R.T.)										
33 (R.T.)										
34 (R.T.)										
35 (R.T.)										
36	680 ^L	14.2 ^L	40.5 ^L	59.6	20.9	35.1 ^H	3.4 ^H	90.0	12.3	18.0 ^H
37	729	15.1	43.2	59.2 ^L	20.7	35.0	1.0 ^L	79.0 ^L	12.0	14.6 ^L
38	721	14.8	43.0	59.6	20.5 ^L	34.4	3.1	92.0	11.1 ^L	17.0
39	701	14.7	43.0	61.4 ^H	21.0	34.2 ^L	2.0	85.3	12.0	17.0
40	737 ^H	15.6 ^H	44.4 ^H	60.3	21.2 ^H	35.1 ^H	2.3	95.4 ^H	12.8 ^H	17.9
N	5	5	5	5	5	5	5	5	5	5
Mean	714	14.9	42.8	60.0	20.9	34.8	2.4	88.3	12.0	16.9
S.D.	23	0.5	1.4	0.9	0.3	0.4	1.0	6.4	0.6	1.4
S.E.	10	0.2	0.6	0.4	0.1	0.2	0.4	2.9	0.3	0.6
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
31 (R.T.)							
32 (R.T.)							
33 (R.T.)							
34 (R.T.)							
35 (R.T.)							
36	55	0	6	0 ^L	0	0 ^L	94 ^H
37	31 ^L	0	11	3 ^H	0	2	84 ^L
38	53	0	12 ^H	0 ^L	0	3	85
39	37	0	6	0 ^L	0	5 ^H	89
40	57 ^H	0	5 ^L	0 ^L	0	3	92
N	5	5	5	5	5	5	5
Mean	47	0	8	1	0	3	89
S.D.	12	0	3	1	0	2	4
S.E.	5	0	1	1	0	1	2
M.C.	B->K		B->A	B->A		B->A	B->A

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T.. for recovery test

L. lowest
 H. highest

M.C.. multiple comparisons
 B. Bartlett's test
 A. analysis of variance
 K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 5-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of dosing period; the dosage of 5 mg/kg

Animal No.	R B C (x10 ⁶ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μ m ³)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
41	672 ^L	14.8	41.3	61.4 ^H	22.0 ^H	35.8	2.9 ^H	88.5 ^L	11.8	15.6 ^L
42	715	14.7	42.0	58.8	20.6	35.0	2.6	93.4	12.3	15.8
43	717	14.9 ^H	40.8	56.9 ^L	20.8	36.5 ^H	1.2 ^L	107.0 ^H	13.1	16.5
44	734 ^H	14.5	42.8 ^H	58.3	19.8 ^L	33.9 ^L	1.8	88.7	11.7 ^L	17.3 ^H
45	705	14.3 ^L	40.6 ^L	57.6	20.3	35.2	2.2	106.2	13.4 ^H	16.2
N	5	5	5	5	5	5	5	5	5	5
Mean	709	14.6	41.5	58.6	20.7	35.3	2.1	96.8	12.5	16.3
S.D.	23	0.2	0.9	1.7	0.8	1.0	0.7	9.2	0.8	0.7
S.E.	10	0.1	0.4	0.8	0.4	0.4	0.3	4.1	0.3	0.3
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
41	57	0	8	0 ^L	0	2	90
42	49	0	3 ^L	1 ^H	0	0 ^L	96 ^H
43	47	0	8	0 ^L	0	1	91
44	21 ^L	0	17 ^H	1 ^H	0	0 ^L	82 ^L
45	71 ^H	0	3 ^L	1 ^H	0	3 ^H	93
N	5	5	5	5	5	5	5
Mean	49	0	8	1	0	1	90
S.D.	18	0	6	1	0	1	5
S.E.	8	0	3	0	0	1	2
M.C.	-----	-----	-----	-----	-----	-----	-----

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T.. for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B. Bartlett's test
 A. analysis of variance

K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 5-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of dosing period; the dosage of 10 mg/kg

Animal No.	R B C ($\times 10^4/\text{mm}^3$)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm^3)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet ($\times 10^4/\text{mm}^3$)	P T (sec)	A P T T (sec)
46	704	14.5 ^L	41.4 ^L	58.8	20.6	35.0 ^H	2.5	106.4	13.0	17.3 ^H
47	689	14.5 ^L	42.2	61.3	21.0	34.4	2.6	95.1 ^L	12.9	13.7
48	744 ^H	15.1	43.2	58.1 ^L	20.3 ^L	35.0 ^H	3.3 ^H	103.4	12.5 ^L	13.3 ^L
49	685 ^L	14.5 ^L	42.1	61.4	21.2 ^H	34.4	1.4	116.8 ^H	13.0	14.7
50	734	15.5 ^H	45.8 ^H	62.4 ^H	21.1	33.8 ^L	1.3 ^L	106.6	13.1 ^H	15.9
N	5	5	5	5	5	5	5	5	5	5
Mean	711	14.8	42.9	60.4	20.8	34.5	2.2	105.7	12.9	15.0
S.D.	27	0.5	1.7	1.8	0.4	0.5	0.9	7.8	0.2	1.6
S.E.	12	0.2	0.8	0.8	0.2	0.2	0.4	3.5	0.1	0.7
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Animal No.	W B C ($\times 100/\text{mm}^3$)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
46	46	0	4 ^L	0 ^L	0	1	95 ^H
47	42	0	8	0 ^L	0	0 ^L	92
48	39 ^L	0	16	1	0	3 ^H	80
49	49 ^H	0	19	2 ^H	0	3 ^H	76
50	45	0	23 ^H	0 ^L	0	2	75 ^L
N	5	5	5	5	5	5	5
Mean	44	0	14	1	0	2	84
S.D.	4	0	8	1	0	1	9
S.E.	2	0	4	0	0	1	4
M.C.	-----	-----	-----	-----	-----	-----	-----

*. significantly different from control, $p < 0.05$
 **. significantly different from control, $p < 0.01$
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test

K, Kruskal-Wallis' H test

A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 5-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of dosing period; the dosage of 20 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (fL)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
51 (R.T.)										
52 (R.T.)										
53 (R.T.)										
54 (R.T.)										
55 (R.T.)										
56	717	14.8	41.0 ^L	57.2 ^L	20.6	36.1 ^H	2.1	93.1	12.4 ^L	13.7 ^L
57	655 ^L	14.3 ^L	41.1	62.7 ^H	21.8 ^H	34.8	2.0	76.5 ^L	13.6 ^H	16.0
58	774 ^H	15.4 ^H	44.3	57.2 ^L	19.9 ^L	34.8	1.3 ^L	104.2	12.6	16.1
59	722	15.4 ^H	44.5 ^H	61.7	21.3	34.6	2.5 ^H	94.8	12.4 ^L	16.3 ^H
60	702	14.3 ^L	41.5	59.1	20.4	34.5 ^L	1.8	115.4 ^H	12.7	16.3 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	714	14.8	42.5	59.6	20.8	35.0	1.9	96.8	12.7	15.7
S.D.	43	0.6	1.8	2.5	0.8	0.7	0.4	14.4	0.5	1.1
S.E.	19	0.2	0.8	1.1	0.3	0.3	0.2	6.4	0.2	0.5
M.C.										

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
51 (R.T.)							
52 (R.T.)							
53 (R.T.)							
54 (R.T.)							
55 (R.T.)							
56	37 ^L	0	9	0 ^L	0	1	90
57	38	0	15 ^H	1 ^H	0	2 ^H	82 ^L
58	39	0	10	0 ^L	0	0 ^L	90
59	46	0	2 ^L	1 ^H	0	1	96
60	48 ^H	0	3	0 ^L	0	0 ^L	97 ^H
N	5	5	5	5	5	5	5
Mean	42	0	8	0	0	1	91
S.D.	5	0	5	1	0	1	6
S.E.	2	0	2	0	0	0	3
M.C.							

*. significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H. highest B. Bartlett's test K. Kruskal-Wallis' H test
 R.T., for recovery test A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

Appendix 5-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of recovery period; the dosage of 0 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μm ³)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
1	809 ^H	15.8 ^H	47.4 ^H	58.6 ^H	19.5	33.3 ^L	1.3 ^L	107.8	15.8	22.4
2	737 ^L	14.8 ^L	42.3 ^L	57.4	20.1 ^H	35.0 ^H	1.3 ^L	114.4 ^H	16.5	18.5 ^L
3	780	15.4	44.4	56.9	19.7	34.7	1.9	112.2	14.8	19.5
4	784	15.1	44.5	56.7 ^L	19.3 ^L	33.9	2.0	98.6	12.7 ^L	19.5
5	774	14.9	44.6	57.6	19.3 ^L	33.4	2.1 ^H	90.0 ^L	19.9 ^H	22.9 ^H
6 (S.S.)										
7 (S.S.)										
8 (S.S.)										
9 (S.S.)										
10 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	777	15.2	44.6	57.4	19.6	34.1	1.7	104.6	15.9	20.6
S.D.	26	0.4	1.8	0.7	0.3	0.8	0.4	10.2	2.6	2.0
S.E.	12	0.2	0.8	0.3	0.1	0.3	0.2	4.5	1.2	0.9

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
1	71	0	2 ^L	0 ^L	0	4 ^H	94
2	105	0	6 ^H	0 ^L	0	1	93 ^L
3	90	0	3	1 ^H	0	2	94
4	60 ^L	0	2 ^L	0 ^L	0	3	95 ^H
5	115 ^H	0	5	0 ^L	0	0 ^L	95 ^H
6 (S.S.)							
7 (S.S.)							
8 (S.S.)							
9 (S.S.)							
10 (S.S.)							
N	5	5	5	5	5	5	5
Mean	88	0	4	0	0	2	94
S.D.	23	0	2	0	0	2	1
S.E.	10	0	1	0	0	1	0

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S.. scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 5-2-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual males at the end of recovery period; the dosage of 20 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (fL)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
21	715 ^L	14.9	42.4 ^L	59.3	20.8	35.1 ^H	4.0 ^H	86.3	12.7 ^L	18.3
22	722	15.2	43.5	60.3 ^H	21.1 ^H	34.9	2.8	99.5 ^H	16.5	19.3
23	735	15.2	43.7	59.5	20.7	34.8	1.8 ^L	90.6	17.1	19.0
24	769 ^H	15.5 ^H	45.2 ^H	58.8	20.2	34.3 ^L	2.1	77.5 ^L	18.2 ^H	21.9 ^H
25	734	14.7 ^L	42.6	58.0 ^L	20.0 ^L	34.5	3.5	93.8	13.1	18.0 ^L
26 (S.S.)										
27 (S.S.)										
28 (S.S.)										
29 (S.S.)										
30 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	735	15.1	43.5	59.2	20.6	34.7	2.8	89.5	15.5	19.3
S.D.	21	0.3	1.1	0.9	0.5	0.3	0.9	8.3	2.5	1.5
S.E.	9	0.1	0.5	0.4	0.2	0.1	0.4	3.7	1.1	0.7
F	1.56	1.74	2.66	1.31	1.81	5.72	5.61	1.51	1.14	1.61
T	2.81*	0.44	1.22	3.44**	3.90**	1.78	2.50*	2.57*	0.26	1.13

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
21	71	0	7	0 ^L	0	7 ^H	86
22	79 ^H	0	6	0 ^L	0	5	89
23	66	0	11	0 ^L	0	1 ^L	88
24	59 ^L	0	2 ^L	1 ^H	0	4	93 ^H
25	62	0	17 ^H	0 ^L	0	7 ^H	76 ^L
26 (S.S.)							
27 (S.S.)							
28 (S.S.)							
29 (S.S.)							
30 (S.S.)							
N	5	5	5	5	5	5	5
Mean	67	0	9	0	0	5	86
S.D.	8	0	6	0	0	1	6
S.E.	4	0	3	0	0	1	3
F	8.41*	Incomplete	9.79*	1.00	Incomplete	2.48	57.57**
T	1.92	-----	1.87	0.00	-----	2.12	2.72

*. significantly different from control, p<0.05 L, lowest
 **. significantly different from control, p<0.01 H, highest
 S.S.. scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 5-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of recovery period; the dosage of 0 mg/kg

Animal No.	R B C (x10 ⁴ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (fL)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
31	783	15.7 ^H	45.6 ^H	58.3 ^H	20.1 ^H	34.4	3.0 ^H	86.0	12.4 ^H	19.0 ^H
32	773	15.3	44.3	57.3	19.8	34.5	1.7 ^L	83.8 ^L	12.4 ^H	16.4 ^L
33	756 ^L	15.1	42.6 ^L	56.4	20.0	35.4 ^H	2.0	97.4	12.4 ^H	17.1
34	763	15.0 ^L	44.3	58.0	19.7	33.9 ^L	3.0 ^H	109.6 ^H	11.6	17.5
35	801 ^H	15.6	45.1	56.3 ^L	19.5 ^L	34.6	2.2	99.9	11.3 ^L	17.3
36 (S.S.)										
37 (S.S.)										
38 (S.S.)										
39 (S.S.)										
40 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	775	15.3	44.4	57.3	19.8	34.6	2.4	95.3	12.0	17.5
S.D.	18	0.3	1.1	0.9	0.2	0.5	0.6	10.6	0.5	1.0
S.E.	8	0.1	0.5	0.4	0.1	0.2	0.3	4.7	0.2	0.4

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
31	49	0	4 ^L	0 ^L	0	7 ^H	89
32	36 ^L	0	6	0 ^L	0	5 ^L	92
33	38	0	9	1 ^H	0	5	85 ^L
34	52 ^H	0	11 ^H	1 ^H	0	3 ^L	86
35	48	0	5	0 ^L	0	2 ^L	93 ^H
36 (S.S.)							
37 (S.S.)							
38 (S.S.)							
39 (S.S.)							
40 (S.S.)							
N	5	5	5	5	5	5	5
Mean	45	0	7	0	0	5	89
S.D.	7	0	3	1	0	2	2
S.E.	3	0	1	0	0	1	2

*, significantly different from control, p<0.05 L, lowest
 **, significantly different from control, p<0.01 H, highest
 S.S., scheduled sacrifice T, Student's t-test or Aspin-Welch's t-test

Appendix 5-2-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Hematological findings in individual females at the end of recovery period; the dosage of 20 mg/kg

Animal No.	R B C (x10 ⁶ /mm ³)	Hemoglobin (g/dL)	Hematocrit (%)	M C V (μ m ³)	M C H (pg)	M C H C (%)	Reticulocyte (%)	Platelet (x10 ⁴ /mm ³)	P T (sec)	A P T T (sec)
51	727	15.0	42.5	58.5	20.6 ^H	35.3 ^H	3.1 ^H	95.2	11.6	15.3
52	722 ^L	14.7	42.3	58.6	20.4	34.8	2.4	89.1	11.2 ^L	16.6 ^H
53	740	14.8	43.2	58.4	20.0	34.3	2.4	84.5 ^L	12.4 ^H	16.6 ^H
54	759 ^H	14.5 ^L	42.1 ^L	55.5 ^L	19.1 ^L	34.4	2.8	100.6 ^H	11.3	15.0 ^L
55	754	15.3 ^H	44.9 ^H	59.6 ^H	20.3	34.1 ^L	2.2 ^L	85.4	11.9	16.2
56 (S.S.)										
57 (S.S.)										
58 (S.S.)										
59 (S.S.)										
60 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	740	14.9	43.0	58.1	20.1	34.6	2.6	91.0	11.7	15.9
S.D.	16	0.3	1.1	1.5	0.6	0.5	0.4	6.8	0.5	0.7
S.E.	7	0.1	0.5	0.7	0.3	0.2	0.2	3.1	0.2	0.3
F	1.19	1.00	1.00	2.89	6.09	1.29	2.67	2.40	1.19	1.64
T	3.25*	2.49*	1.91	1.08	0.91	0.06	0.64	0.78	1.06	2.80*

Animal No.	W B C (x100/mm ³)	Band neutrophil (%)	Segmented neutrophil (%)	Eosinophil (%)	Basophil (%)	Monocyte (%)	Lymphocyte (%)
51	54 ^H	0	8	1	0	8 ^H	83
52	31 ^L	0	19 ^H	2 ^H	0	3	76 ^L
53	31 ^L	0	3 ^L	0 ^L	0	1 ^L	96 ^H
54	45	0	8	0 ^L	0	1 ^L	91
55	34	0	7	0 ^L	0	2	91
56 (S.S.)							
57 (S.S.)							
58 (S.S.)							
59 (S.S.)							
60 (S.S.)							
N	5	5	5	5	5	5	5
Mean	39	0	9	1	0	3	87
S.D.	10	0	6	1	0	3	8
S.E.	5	0	3	0	0	1	4
F	2.04	Incomplete	4.18	2.67	Incomplete	1.60	4.98
T	1.01	-----	0.67	0.43	-----	0.36	0.41

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S.. scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 6-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Total Protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
1 (R.T.)										
2 (R.T.)										
3 (R.T.)										
4 (R.T.)										
5 (R.T.)										
6	5.6 ^H	3.1 ^H	1.24	139 ^H	38	42	15	0.6 ^H	8.1 ^H	9.0 ^H
7	5.0 ^L	3.0	1.50 ^H	139 ^H	35 ^L	46 ^H	14 ^L	0.5 ^L	7.3	8.8
8	5.2	3.1 ^H	1.48	121 ^L	39	36 ^L	18	0.5 ^L	7.4	8.9
9	5.3	2.9 ^L	1.21 ^L	135	46 ^H	41	21 ^H	0.5 ^L	7.5	8.6 ^L
10	5.0 ^L	2.9 ^L	1.38	131	41	42	18	0.5 ^L	7.1 ^L	8.6 ^L
N	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.0	1.36	133	40	41	17	0.5	7.5	8.8
S.D.	0.2	0.1	0.13	7	4	4	3	0.0	0.4	0.2
S.E.	0.1	0.0	0.06	3	2	2	1	0.0	0.2	0.1
M.C.	B->A	B->A	B->A	B->A	B->A	B->K	B->A	B->A	B->A	B->A

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
1 (R.T.)							
2 (R.T.)							
3 (R.T.)							
4 (R.T.)							
5 (R.T.)							
6	144.9 ^L	3.62	106.4	533 ^H	34 ^H	75 ^H	0 ^L
7	145.3	3.60	106.1 ^L	406	24 ^L	68	0 ^L
8	145.2	3.66 ^H	107.7	438	33	73	0 ^L
9	146.4 ^H	3.32 ^L	108.3	500	25	67	0 ^L
10	146.4 ^H	3.39	108.4 ^H	389 ^L	27	61 ^L	1 ^H
N	5	5	5	5	5	5	5
Mean	145.6	3.52	107.4	453	29	69	0
S.D.	0.7	0.15	1.1	62	5	5	0
S.E.	0.3	0.07	0.5	28	2	2	0
M.C.	B->A	B->A	B->A	B->A	B->K	B->A	K

*, significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H. highest B. Bartlett's test K. Kruskal-Wallis' H test
 R.T., for recovery test A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

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Appendix 6-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
11	5.1	3.2 ^H	1.68 ^H	123 ^L	31	31 ^L	16	0.5 ^L	7.2 ^L	9.0
12	5.4 ^H	3.0	1.25	123 ^L	34	32	14 ^L	0.6 ^H	7.3	9.0
13	5.2	2.8 ^L	1.17 ^L	130 ^H	42 ^H	39	17	0.6 ^H	7.2 ^L	8.6 ^L
14	5.0 ^L	2.8 ^L	1.27	123 ^L	41	54 ^H	14 ^L	0.6 ^L	7.7 ^H	8.7
15	5.0 ^L	3.0	1.50	127	30 ^L	36	18 ^H	0.5 ^L	7.5	9.1 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	5.1	3.0	1.37	125	36	42	16	0.5	7.4	8.9
S.D.	0.2	0.2	0.21	3	6	10	2	0.1	0.2	0.2
S.E.	0.1	0.1	0.09	1	3	5	1	0.0	0.1	0.1
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
11	144.6	3.61	107.8	317 ^L	31 ^H	60 ^L	0
12	143.9 ^L	3.80 ^H	105.8 ^L	556 ^H	29	62	0
13	145.6 ^H	3.53	107.9	445	29	74 ^H	0
14	145.4	3.48 ^L	108.2 ^H	336	29	68	0
15	145.5	3.62	106.1	473	28 ^L	64	0
N	5	5	5	5	5	5	5
Mean	145.0	3.61	107.2	425	29	66	0
S.D.	0.7	0.12	1.1	99	1	6	0
S.E.	0.3	0.05	0.5	44	0	2	0
M.C.							

*, significantly different from control, P<0.05
 **, significantly different from control, P<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 6-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Total Protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
16	5.1 ^L	2.8 ^L	1.22	120 ^L	44	60	14	0.6 ^H	7.8 ^H	8.6 ^L
17	5.4	2.9	1.16 ^L	127	34 ^L	32	23 ^H	0.6 ^H	7.4	8.9
18	5.5 ^H	3.2 ^H	1.39	135 ^H	46	63 ^H	15	0.5 ^L	7.4	8.9
19	5.4	3.2 ^H	1.45 ^H	126	50 ^H	36	13 ^L	0.5 ^L	7.7	9.1 ^H
20	5.2	2.9	1.26	121	42	23 ^L	16	0.6 ^H	7.0 ^L	8.9
N	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.0	1.30	126	43	43	16	0.6	7.5	8.9
S.D.	0.2	0.2	0.12	6	6	18	4	0.1	0.3	0.2
S.E.	0.1	0.1	0.05	3	3	8	2	0.0	0.1	0.1
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
16	144.9	3.84	107.3	325 ^L	27	65	0
17	145.1 ^H	4.06 ^H	108.7 ^H	450	26 ^L	54 ^L	0
18	144.5 ^L	3.45 ^L	105.3 ^L	479 ^H	33 ^H	68 ^H	0
19	144.6	3.67	107.7	358	28	62	0
20	145.1 ^H	3.65	108.0	366	32	57	0
N	5	5	5	5	5	5	5
Mean	144.8	3.73	107.4	396	29	61	0
S.D.	0.3	0.23	1.3	66	3	6	0
S.E.	0.1	0.10	0.6	29	1	3	0
M.C.							

*. significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

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Appendix 6-1-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of dosing period; the dosage of 20 mg/kg

Animal No.	Total Protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
21 (R.T.)										
22 (R.T.)										
23 (R.T.)										
24 (R.T.)										
25 (R.T.)										
26	5.4	3.3 ^H	1.57 ^H	120 ^L	40 ^L	36	19 ^H	0.6 ^H	7.8 ^H	9.2 ^H
27	5.1	3.1	1.55	136	50 ^H	44 ^H	18	0.6 ^H	7.5	9.0
28	5.6 ^H	3.2	1.33 ^L	145 ^H	50 ^H	36	15 ^L	0.5 ^L	6.2 ^L	9.1
29	5.0 ^L	3.0 ^L	1.50	123	40 ^L	30 ^L	16	0.6 ^H	7.6	8.9 ^L
30	5.5	3.2	1.39	126	41	38	15 ^L	0.6 ^H	7.2	9.0
N	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.2	1.47	130	44	37	17	0.6	7.3	9.0
S.D.	0.3	0.1	0.10	10	5	5	2	0.0	0.6	0.1
S.E.	0.1	0.1	0.05	5	2	2	1	0.0	0.3	0.1
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
21 (R.T.)							
22 (R.T.)							
23 (R.T.)							
24 (R.T.)							
25 (R.T.)							
26	144.5 ^L	3.93 ^H	107.6	272 ^L	28	52 ^L	0 ^L
27	145.0	3.70	108.8	402	43 ^H	87 ^H	0 ^L
28	144.7	3.45 ^L	106.5 ^L	402	40	60	1 ^H
29	146.1 ^H	3.63	109.7 ^H	426	34	70	0 ^L
30	145.5	3.46	108.7	492 ^H	26 ^L	66	0 ^L
N	5	5	5	5	5	5	5
Mean	145.2	3.63	108.3	399	34	67	0
S.D.	0.6	0.20	1.2	80	7	13	0
S.E.	0.3	0.09	0.6	36	3	6	0
M.C.							

*, significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 6-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. phos. (mg/dL)	Ca (mg/dL)
31 (R.T.)										
32 (R.T.)										
33 (R.T.)										
34 (R.T.)										
35 (R.T.)										
36	5.4 ^H	3.2	1.45 ^L	116 ^L	50	36 ^H	14 ^L	0.6	5.1 ^L	8.4 ^L
37	5.2	3.1	1.48	139 ^H	53 ^H	28	18 ^H	0.6	5.7	8.6
38	5.4 ^H	3.4 ^H	1.70 ^H	120	53 ^H	33	15	0.6	5.3	8.8 ^H
39	5.2	3.2	1.60	117	51	20 ^L	18 ^H	0.6	5.9	8.8 ^H
40	4.8 ^L	3.0 ^L	1.67	131	43 ^L	35	17	0.6	7.2 ^H	8.8 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.2	1.58	125	50	30	16	0.6	5.8	8.7
S.D.	0.2	0.1	0.11	10	4	7	2	0.0	0.8	0.2
S.E.	0.1	0.1	0.05	4	2	3	1	0.0	0.4	0.1
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	K	B->A	B->A

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
31 (R.T.)							
32 (R.T.)							
33 (R.T.)							
34 (R.T.)							
35 (R.T.)							
36	143.7	3.43	108.8	321	19	62	0 ^L
37	142.3 ^L	3.23	107.4 ^L	154 ^L	21	57 ^L	1 ^H
38	143.7	3.23	109.3 ^H	270	22 ^H	69 ^H	1 ^H
39	143.4	3.45 ^H	108.3	180	21	59	0 ^L
40	144.9 ^H	2.97 ^L	109.2	369 ^H	16 ^L	63	0 ^L
N	5	5	5	5	5	5	5
Mean	143.6	3.26	108.6	259	20	62	0
S.D.	0.9	0.19	0.8	91	2	5	1
S.E.	0.4	0.09	0.3	41	1	2	0
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	K

*, significantly different from control, p<0.05
 **, significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test

A, analysis of variance

K, Kruskal-Wallis' H test

D, Dunnett's test or Dunnett type mean rank test

Appendix 6-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
41	5.6 ^H	3.3	1.43 ^L	136 ^H	54	31	16 ^L	0.6 ^L	6.2	9.1 ^H
42	5.1 ^L	3.2 ^L	1.68	126	40 ^L	20 ^L	17	0.6 ^L	7.1	9.0
43	5.3	3.4	1.79 ^H	110 ^L	55 ^H	27	18	0.6 ^L	5.7 ^L	8.6 ^L
44	5.6 ^H	3.5 ^H	1.67	114	52	33	22	0.6 ^L	7.2 ^H	8.9
45	5.2	3.3	1.74	125	54	37 ^H	24 ^H	0.7 ^H	6.7	8.9
N	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.3	1.66	122	51	30	19	0.6	6.6	8.9
S.D.	0.2	0.1	0.14	10	6	6	3	0.0	0.6	0.2
S.E.	0.1	0.1	0.06	5	3	3	2	0.0	0.3	0.1
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
41	143.4	3.52	108.7	159 ^L	25	55	0
42	143.7	3.44	110.5 ^H	172	29 ^H	61 ^H	0
43	141.9 ^L	3.43	107.0 ^L	343 ^H	20 ^L	58	0
44	144.7	3.87 ^H	109.3	230	23	52 ^L	0
45	145.3 ^H	3.07 ^L	108.4	316	24	61 ^H	0
N	5	5	5	5	5	5	5
Mean	143.8	3.47	108.8	244	24	57	0
S.D.	1.3	0.29	1.3	83	3	4	0
S.E.	0.6	0.13	0.6	37	1	2	0
M.C.							

*. significantly different from control. p<0.05
 **. significantly different from control. p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons

B. Bartlett's test

A. analysis of variance

K. Kruskal-Wallis' H test

D. Dunnett's test or Dunnett type mean rank test

Appendix 6-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Total Protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
46	4.9 ^L	3.0	1.58	113	46	26	14	0.6	5.0 ^L	7.9 ^L
47	4.9 ^L	2.9 ^L	1.45 ^L	119	34 ^L	21 ^L	13 ^L	0.6	5.4	8.6
48	5.0	3.2	1.78	108 ^L	68 ^H	36	18	0.6	5.1	8.7
49	5.3	3.4 ^H	1.79 ^H	131 ^H	58	38 ^H	15	0.6	6.1	8.8
50	5.4 ^H	3.4 ^H	1.70	127	54	35	20 ^H	0.6	7.3 ^H	9.1 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	5.1	3.2	1.66	120	52	31	16	0.6	5.8	8.6
S.D.	0.2	0.2	0.14	10	13	7	3	0.0	1.0	0.4
S.E.	0.1	0.1	0.06	4	6	3	1	0.0	0.4	0.2
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
46	144.7	3.37	109.7	320	19 ^L	49 ^L	0
47	145.4 ^H	3.13 ^L	112.1 ^H	288	24	58	0
48	143.1 ^L	3.54	107.2 ^L	217	28 ^H	59	0
49	144.2	3.58 ^H	109.2	353 ^H	25	61 ^H	0
50	145.2	3.28	109.5	202 ^L	25	58	0
N	5	5	5	5	5	5	5
Mean	144.5	3.38	109.5	276	24	57	0
S.D.	0.9	0.19	1.7	65	3	5	0
S.E.	0.4	0.08	0.8	29	1	2	0
M.C.							

*. significantly different from control. p<0.05
 **, significantly different from control. p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test

A, analysis of variance

K, Kruskal-Wallis' H test

D, Dunnett's test or Dunnett type mean rank test

Appendix 6-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of dosing period; the dosage of 20 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. phos. (mg/dL)	Ca (mg/dL)
51 (R.T.)										
52 (R.T.)										
53 (R.T.)										
54 (R.T.)										
55 (R.T.)										
56	4.5 ^L	2.8 ^L	1.65	120	67 ^H	53 ^H	21	0.6 ^L	6.5 ^H	8.3 ^L
57	4.8	3.0	1.67	125 ^H	45 ^L	25	16	0.6 ^L	6.2 ^L	8.4
58	4.9	3.1	1.72	110 ^L	46	27	19	0.7 ^H	6.1 ^L	8.5
59	5.2	3.1	1.48 ^L	113	63	25	15 ^L	0.6 ^L	6.5 ^H	8.6
60	5.3 ^H	3.4 ^H	1.79 ^H	121	57	22 ^L	25 ^H	0.7 ^H	6.3	8.8 ^H
N	5	5	5	5	5	5	5	5	5	5
Mean	4.9	3.1	1.66	118	56	30	19	0.6	6.3	8.5
S.D.	0.3	0.2	0.12	6	10	13	4	0.1	0.2	0.2
S.F.	0.1	0.1	0.05	3	4	6	2	0.0	0.1	0.1
M.C.										

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
51 (R.T.)							
52 (R.T.)							
53 (R.T.)							
54 (R.T.)							
55 (R.T.)							
56	142.5 ^L	3.87 ^H	110.2	258	24	57	0 ^L
57	145.3	2.95 ^L	107.4 ^L	331	33 ^H	60	0 ^L
58	143.9	3.49	109.7	307	18 ^L	62 ^H	1 ^H
59	145.7	3.04	109.7	222 ^L	24	59	0 ^L
60	146.0 ^H	3.20	110.4 ^H	346 ^H	26	54 ^L	1 ^H
N	5	5	5	5	5	5	5
Mean	144.7	3.31	109.5	293	25	58	0
S.D.	1.5	0.37	1.2	52	5	3	1
S.F.	0.7	0.17	0.5	23	2	1	0
M.C.							

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons
 B. Bartlett's test
 A. analysis of variance

K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 6-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
1	5.6 ^H	3.3 ^H	1.43	225 ^H	55 ^H	48	16	0.9 ^H	7.8	8.9
2	5.5	3.3 ^H	1.50 ^H	148	55 ^H	50	14	0.6 ^L	6.8 ^L	9.1 ^H
3	5.5	3.3 ^H	1.50 ^H	123 ^L	52	56 ^H	14	0.7	7.3	8.8
4	5.4 ^L	3.0 ^L	1.25 ^L	151	33 ^L	33 ^L	20 ^H	0.6 ^L	6.9	8.7 ^L
5	5.5	3.1	1.29	187	35	52	13 ^L	0.7	8.0 ^H	9.1 ^H
6 (S.S.)										
7 (S.S.)										
8 (S.S.)										
9 (S.S.)										
10 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.2	1.39	167	46	48	15	0.7	7.4	8.9
S.D.	0.1	0.1	0.12	40	11	9	3	0.1	0.5	0.2
S.E.	0.0	0.1	0.05	18	5	4	1	0.1	0.2	0.1

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
1	144.8	4.04	106.4	372 ^H	27	74	0
2	145.5	3.80	108.0 ^H	369	25 ^L	62 ^L	0
3	147.2 ^H	3.71 ^L	106.8	267	27	64	0
4	145.5	3.79	106.4	321	39 ^H	80 ^H	0
5	143.3 ^L	4.79 ^H	104.9 ^L	264 ^L	32	68	0
6 (S.S.)							
7 (S.S.)							
8 (S.S.)							
9 (S.S.)							
10 (S.S.)							
N	5	5	5	5	5	5	5
Mean	145.3	4.03	106.5	319	30	70	0
S.D.	1.4	0.44	1.1	53	6	7	0
S.E.	0.6	0.20	0.5	23	3	3	0

*. significantly different from control, p<0.05 L, lowest
 **. significantly different from control, p<0.01 H, highest
 S.S., scheduled sacrifice T, Student's t-test or Aspin-Welch's t-test

Appendix 6-2-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual males at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
21	5.2	3.0 ^L	1.36 ^L	142	46 ^H	36 ^L	15	0.6 ^L	7.4	8.7 ^L
22	5.1 ^L	3.1	1.55	170 ^H	37	44	11 ^L	0.7 ^H	7.4	9.2 ^H
23	5.3 ^H	3.3 ^H	1.65 ^H	145	34 ^L	61 ^H	13	0.7 ^H	6.3 ^L	8.9
24	5.3 ^H	3.1	1.41	150	36	46	15	0.6 ^L	7.0	9.1
25	5.1 ^L	3.1	1.55	130 ^L	46 ^H	61 ^H	16 ^H	0.6 ^L	7.6 ^H	8.9
26 (S.S.)										
27 (S.S.)										
28 (S.S.)										
29 (S.S.)										
30 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.1	1.50	147	40	50	14	0.6	7.1	9.0
S.D.	0.1	0.1	0.12	15	6	11	2	0.1	0.5	0.2
S.E.	0.0	0.0	0.05	7	3	5	1	0.0	0.2	0.1
F	2.00	1.67	1.00	7.39*	3.67	1.58	1.95	5.00	1.06	1.19
T	5.48**	1.00	1.48	1.02	1.11	0.28	0.91	1.00	0.66	0.34

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
21	145.1	3.98 ^H	106.0	335	30	70	0 ^L
22	144.1 ^L	3.53	106.4	249 ^L	28 ^L	68	1 ^H
23	144.6	3.55	106.1	370 ^H	29	63 ^L	0 ^L
24	145.5	3.30 ^L	105.9 ^L	320	33 ^H	79 ^H	0 ^L
25	146.0 ^H	3.69	107.1 ^H	273	28 ^L	69	0 ^L
26 (S.S.)							
27 (S.S.)							
28 (S.S.)							
29 (S.S.)							
30 (S.S.)							
N	5	5	5	5	5	5	5
Mean	145.1	3.61	106.3	309	30	70	0
S.D.	0.7	0.25	0.5	49	2	6	0
S.E.	0.3	0.11	0.2	22	1	3	0
F	3.59	3.17	5.23	1.17	7.44*	1.63	Incomplete
T	0.28	1.82	0.37	0.29	0.15	0.05	-----

*. significantly different from control. p<0.05 L. lowest
 **. significantly different from control. p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 6-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
31	5.8	3.2 ^L	1.23 ^L	117 ^L	63 ^H	28	16 ^L	0.8 ^H	5.4	9.5 ^H
32	5.5 ^L	3.6	1.89 ^H	150 ^H	57	38	23 ^H	0.8 ^H	7.0 ^H	8.8 ^L
33	5.8	3.5	1.52	118	42 ^L	24 ^L	21	0.7 ^L	5.3 ^L	9.0
34	6.2 ^H	3.9 ^H	1.70	135	43	79 ^H	23 ^H	0.7 ^L	6.5	9.2
35	5.7	3.6	1.71	129	58	38	21	0.7 ^L	5.9	8.9
36 (S.S.)										
37 (S.S.)										
38 (S.S.)										
39 (S.S.)										
40 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.6	1.61	130	53	41	21	0.7	6.0	9.1
S.D.	0.3	0.3	0.25	14	10	22	3	0.1	0.7	0.3
S.E.	0.1	0.1	0.11	6	4	10	1	0.0	0.3	0.1

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
31	146.2 ^H	4.39 ^H	109.3	190	22 ^L	70	1
32	143.2 ^L	4.05	103.4 ^L	187	22 ^L	63	1
33	144.5	4.24	109.4 ^H	208 ^H	25	71 ^H	1
34	143.5	3.95	106.9	164 ^L	24	51 ^L	1
35	143.8	3.58 ^L	108.4	182	29 ^H	66	1
36 (S.S.)							
37 (S.S.)							
38 (S.S.)							
39 (S.S.)							
40 (S.S.)							
N	5	5	5	5	5	5	5
Mean	144.2	4.04	107.5	186	24	64	1
S.D.	1.2	0.31	2.5	16	3	8	0
S.E.	0.5	0.14	1.1	7	1	4	0

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 6-2-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Biochemical findings in individual females at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Total protein (g/dL)	Albumin (g/dL)	A/G	Glucose (mg/dL)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Inorg. Phos. (mg/dL)	Ca (mg/dL)
51	5.9 ^H	3.6	1.57	113	63	23	18 ^L	0.7 ^L	6.0	9.3 ^H
52	5.7	3.7 ^H	1.85 ^H	109	62	25	20	0.7 ^L	6.3	8.9
53	5.3 ^L	3.2 ^L	1.52 ^L	108 ^L	62	23	22 ^H	0.8 ^H	5.3 ^L	8.5 ^L
54	5.6	3.4	1.55	142 ^H	66 ^H	45 ^H	21	0.7 ^L	5.7	9.2
55	5.4	3.3	1.57	123	55 ^L	19 ^L	18 ^L	0.7 ^L	7.5 ^H	8.8
56 (S.S.)										
57 (S.S.)										
58 (S.S.)										
59 (S.S.)										
60 (S.S.)										
N	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.4	1.61	119	62	27	20	0.7	6.2	8.9
S.D.	0.2	0.2	0.13	14	4	10	2	0.0	0.8	0.3
S.E.	0.1	0.1	0.06	6	2	5	1	0.0	0.4	0.1
F	1.14	1.47	3.44	1.09	5.54	4.53	2.56	1.50	1.32	1.34
T	1.41	0.82	0.02	1.23	1.95	1.33	0.66	0.63	0.28	0.74

Animal No.	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	ALP (U/L)	GPT (U/L)	GOT (U/L)	γ-GTP (U/L)
51	145.0	4.25 ^H	108.7	163	22	55 ^L	1 ^H
52	145.4	4.24	109.2	149 ^L	24	62	0 ^L
53	145.4	3.73	109.7 ^H	173	38 ^H	89 ^H	0 ^L
54	143.2 ^L	3.78	107.5 ^L	246 ^H	25	61	0 ^L
55	146.8 ^H	3.43 ^L	109.4	223	21 ^L	57	0 ^L
56 (S.S.)							
57 (S.S.)							
58 (S.S.)							
59 (S.S.)							
60 (S.S.)							
N	5	5	5	5	5	5	5
Mean	145.2	3.89	108.9	191	26	65	0
S.D.	1.3	0.35	0.9	42	7	14	0
S.E.	0.6	0.16	0.4	19	3	6	0
F	1.16	1.31	8.33*	6.92*	5.72	2.96	Incomplete
T	1.17	0.74	1.20	0.23	0.48	0.08	-----

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

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Appendix 7-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney (R) (mg)	Kidney (L) (mg)	Spleen (mg)
1 (R.H.H.)									
2 (R.H.H.)									
3 (R.H.H.)									
4 (R.H.H.)									
5 (R.H.H.)									
6 (R.H.H.)									
7	366.2 ^H	1951.6	720.9 ^H	1273.6	11714.4 ^H	2714.2	1341.9	1372.3 ^H	726.2
8	341.9	1820.4 ^L	563.9	1276.0	10405.9	2375.4 ^L	1193.6 ^L	1181.8 ^L	725.5
9	348.4	1855.2	706.4	1376.8 ^H	10008.3	2618.8	1319.6	1299.2	823.5 ^H
10	352.7	1881.6	604.7	1188.0	10603.7	2660.4	1368.0	1292.4	622.1 ^L
	324.3 ^L	1973.4 ^H	511.6 ^L	1185.3 ^L	9971.5 ^L	2749.4 ^H	1394.8 ^H	1354.6	721.4
N	5	5	5	5	5	5	5	5	5
Mean	348.7	1896.4	621.5	1259.9	10540.8	2623.6	1323.6	1300.1	723.7
S.D.	16.9	64.6	90.5	78.9	708.4	147.9	77.9	74.6	71.2
S.E.	7.6	28.9	40.5	35.2	316.8	66.0	34.9	33.3	31.9
M.C.	B->A	B->A	B->A	B->A->D	B->A	B->A	B->A	B->A	B->A

Animal No.	Adrenal glands (mg)	Adrenal gland (R) (mg)	Adrenal gland (L) (mg)	Testes (mg)	Testis (R) (mg)	Testis (L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
1 (R.T.)									
2 (R.T.)									
3 (R.T.)									
4 (R.T.)									
5 (R.T.)									
6 (R.T.)									
7	40.8 ^L	19.8 ^L	21.0 ^L	2838.6 ^L	1405.9 ^L	1432.7 ^L	706.3	362.0	344.3
8	77.2 ^H	40.6 ^H	36.6 ^H	3039.8	1495.9	1543.9	763.4 ^H	375.8	387.6 ^H
9	57.8	28.0	29.8	3635.9 ^H	2115.0 ^H	1520.9	687.1 ^L	358.5	328.6 ^L
10	59.3	28.0	31.3	3175.4	1534.7	1640.7 ^H	718.5	344.8 ^L	373.7
	59.6	30.2	29.4	3106.7	1572.2	1534.5	738.8	379.4 ^H	359.4
N	5	5	5	5	5	5	5	5	5
Mean	58.9	29.3	29.6	3159.3	1624.7	1534.5	722.8	364.1	358.7
S.D.	12.9	7.5	5.6	294.7	280.9	74.0	29.5	14.0	23.3
S.E.	5.8	3.3	2.5	131.8	125.6	33.1	13.2	6.2	10.4
M.C.	B->A	B->A	B->K	B->A	B->K	B->A	B->A	B->A	B->A

*. significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H. highest B. Bartlett's test
 R.T., for recovery test A. analysis of variance K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 7-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
11	317.4	1930.7	581.8	1110.4	9629.8	2711.5 ^H	1357.2 ^H	1354.3 ^H	692.1
12	330.8	1866.8	761.1 ^H	1003.2 ^L	10259.9	2474.4	1242.3	1232.1	725.7
13	360.2 ^H	2038.8 ^H	564.2	1199.7 ^H	11249.6 ^H	2451.1	1247.8	1203.3	680.9
14	294.2 ^L	1923.4	542.0	1026.9	8776.2 ^L	2188.8 ^L	1099.5 ^L	1089.3 ^L	479.8 ^L
15	328.0	1820.2 ^L	455.1 ^L	1091.6	9721.3	2394.5	1177.7	1216.8	767.2 ^H
N	5	5	5	5	5	5	5	5	5
Mean	326.1	1916.0	580.5	1086.4	9927.4	2444.1	1224.9	1219.2	669.1
S.D.	23.9	82.1	111.0	77.3	910.4	187.2	95.2	94.3	111.1
S.E.	10.7	36.7	50.0	34.6	407.1	83.7	42.6	42.2	49.7
M.C.				3.31*					

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Testes (mg)	Testis(R) (mg)	Testis(L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
11	41.8	20.2	21.6	2859.2	1424.7	1434.5	685.2 ^L	350.5	334.7 ^L
12	40.2 ^L	19.4 ^L	20.9 ^L	2920.6	1458.4	1462.2	685.2 ^L	336.7	348.5
13	50.7	23.5	27.2 ^H	2802.5 ^L	1400.3 ^L	1402.2 ^L	704.6	330.8 ^L	373.8 ^H
14	43.8	21.8	22.0	3026.6	1513.2	1513.4	691.5	356.5 ^H	335.0
15	51.9 ^H	26.5 ^H	25.0	3103.7 ^H	1545.9 ^H	1557.8 ^H	710.1 ^H	353.9	356.2
N	5	5	5	5	5	5	5	5	5
Mean	45.0	22.3	23.0	2942.8	1468.5	1474.0	695.3	345.7	349.6
S.D.	5.3	2.8	2.4	122.0	60.5	62.1	11.4	11.3	16.3
S.E.	2.3	1.3	1.2	54.8	27.1	27.8	5.1	5.0	7.3
M.C.									

*. significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

Appendix 7-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney (R) (mg)	Kidney (L) (mg)	Spleen (mg)
16	344.2	1944.5	869.8 ^H	1079.8	10242.7	2268.3 ^L	1115.7 ^L	1152.6	563.5
17	312.2 ^L	1944.9	594.8	993.7	9665.4 ^L	2271.4	1130.3	1141.1 ^L	537.6 ^L
18	340.1	1951.2	669.6	1247.7 ^H	10586.9 ^H	2549.0	1298.4	1250.6	685.4
19	349.5 ^H	1951.9 ^H	654.7	1075.3	10175.8	2633.4 ^H	1319.0 ^H	1314.4 ^H	707.6
20	324.2	1823.4 ^L	417.6 ^L	988.6 ^L	10341.9	2526.3	1238.8	1287.5	855.9 ^H
N	5	5	5	5	5	5	5	5	5
Mean	334.0	1923.2	641.3	1077.0	10202.5	2449.7	1220.4	1229.2	670.0
S.D.	15.4	55.9	162.3	104.8	338.4	168.9	93.8	78.7	127.6
S.E.	6.9	25.0	72.6	46.9	151.3	75.6	42.0	35.2	57.0
M.C.	-----	-----	-----	3.49**	-----	-----	-----	-----	-----

Animal No.	Adrenal glands (mg)	Adrenal gland (R) (mg)	Adrenal gland (L) (mg)	Testes (mg)	Testis (R) (mg)	Testis (L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
16	48.9	23.2	25.7	3038.3	1526.5	1511.8	644.6 ^L	333.6 ^L	311.0 ^L
17	45.2 ^L	21.4 ^L	23.8 ^L	2866.8 ^L	1458.5 ^L	1408.3 ^L	681.0	341.8	339.2
18	51.6	25.8	25.8 ^H	3088.8	1564.1	1524.7	735.6	374.5	361.1
19	48.3	23.9	24.4	2954.5	1470.3	1484.2	777.7 ^H	399.8 ^H	377.9 ^H
20	54.0 ^H	28.2 ^H	25.8 ^H	3203.7 ^H	1617.8 ^H	1585.9 ^H	699.0	349.2	349.8
N	5	5	5	5	5	5	5	5	5
Mean	49.6	24.5	25.1	3030.4	1527.4	1503.0	707.6	359.8	347.8
S.D.	3.4	2.6	0.9	128.5	66.2	64.7	51.1	27.1	25.1
S.E.	1.5	1.2	0.4	57.5	29.6	28.9	22.9	12.1	11.2
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	-----

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons

B. Bartlett's test
 A. analysis of variance

K. Kruskal-Wallis' H test

D. Dunnett's test or Dunnett type mean rank test

Appendix 7-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of dosing period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
21 (R.T.)									
22 (R.T.)									
23 (R.T.)									
24 (R.T.)									
25 (R.T.)									
26	324.5	1948.4	521.2	1049.5	9871.7	2597.2	1287.3	1309.9	608.8
27	331.5	1921.1	701.1 ^H	972.6 ^L	10248.9	2288.1	1116.6 ^L	1171.5	524.5 ^L
28	338.5 ^H	1914.8	516.2	1047.9	11531.3 ^H	2579.2	1312.5	1266.7	825.8 ^H
29	297.3 ^L	1733.4 ^L	472.6 ^L	1002.6	8259.2 ^L	2245.2 ^L	1147.4	1097.8 ^L	563.0
30	336.7	2078.1 ^H	490.2	1145.2 ^H	9804.4	2657.1 ^H	1337.5 ^H	1319.6 ^H	742.7
N	5	5	5	5	5	5	5	5	5
Mean	325.7	1919.2	540.3	1043.6	9943.1	2473.4	1240.3	1233.1	653.0
S.D.	16.8	123.1	92.1	65.4	1170.0	191.5	101.0	95.7	127.0
S.E.	7.5	55.1	41.2	29.2	523.2	85.6	45.2	42.8	56.8
M.C.				4.13**					

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Testes (mg)	Testis(R) (mg)	Testis(L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
21 (R.T.)									
22 (R.T.)									
23 (R.T.)									
24 (R.T.)									
25 (R.T.)									
26	57.0	26.4	30.6	3106.5 ^H	1557.5 ^H	1549.0 ^H	710.2	359.6	350.6
27	60.5 ^H	29.7 ^H	30.8 ^H	2891.7	1397.3	1494.4	688.6	346.8	341.8
28	55.6	26.6	29.0	3012.0	1508.3	1503.7	640.2 ^L	314.8 ^L	325.4 ^L
29	43.3 ^L	21.5 ^L	21.8 ^L	2702.5 ^L	1334.7 ^L	1367.8 ^L	668.2	331.2	337.0
30	59.8	29.6	30.2	3032.6	1527.5	1505.1	772.6 ^H	395.6 ^H	377.0 ^H
N	5	5	5	5	5	5	5	5	5
Mean	55.2	26.8	28.5	2949.1	1465.1	1484.0	696.0	349.6	346.4
S.D.	7.0	3.3	3.8	158.0	94.7	68.3	50.0	30.7	19.4
S.E.	3.1	1.5	1.7	70.6	42.4	30.6	22.4	13.7	8.7
M.C.									

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test

A, analysis of variance

K, Kruskal-Wallis' H test

D, Dunnett's test or Dunnett type mean rank test

Appendix 7-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
31 (R.T.)									
32 (R.T.)									
33 (R.T.)									
34 (R.T.)									
35 (R.T.)									
36	208.3	1762.7	461.8	705.2 ^L	6438.6	1706.7	837.2	869.5	517.6
37	216.0	1735.5 ^L	464.1	757.3	6313.9	1660.3 ^L	821.5	838.8	528.5
38	230.6 ^H	1911.3 ^H	519.3	860.2 ^H	6943.7 ^H	1854.2 ^H	910.0 ^H	944.2 ^H	502.8 ^L
39	201.8 ^L	1778.8	435.2 ^L	794.6	6244.5 ^L	1677.6	873.2	804.4 ^L	538.3 ^H
40	216.7	1838.0	614.6 ^H	739.0	6556.7	1669.9	813.9 ^L	856.0	522.0
N	5	5	5	5	5	5	5	5	5
Mean	214.7	1805.3	499.0	771.3	6499.5	1713.7	851.2	862.6	521.8
S.D.	10.8	70.2	71.5	59.3	275.6	80.4	40.0	51.7	13.2
S.E.	4.8	31.4	32.0	26.5	123.2	36.0	17.9	23.1	5.9
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->K

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Ovaries (mg)	Ovary(R) (mg)	Ovary(L) (mg)
31 (R.T.)						
32 (R.T.)						
33 (R.T.)						
34 (R.T.)						
35 (R.T.)						
36	56.7	27.9	28.8	72.8 ^L	32.7 ^L	40.1
37	57.7	28.5	29.2	86.7	41.5	45.2
38	73.1 ^H	34.5 ^H	38.6 ^H	107.1 ^H	53.6 ^H	53.5 ^H
39	52.1 ^L	25.4 ^L	26.7 ^L	87.3	50.9	36.4 ^L
40	67.8	33.8	34.0	85.4	43.2	42.2
N	5	5	5	5	5	5
Mean	61.5	30.0	31.5	87.9	44.4	43.5
S.D.	8.7	4.0	4.8	12.3	8.3	6.5
S.E.	3.9	1.8	2.1	5.5	3.7	2.9
M.C.	B->A	B->A	B->A	B->A	B->A	B->A

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 7-1-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney (R) (mg)	Kidney (L) (mg)	Spleen (mg)
41	242.2 ^H	1737.9	556.9	866.6 ^H	7978.8 ^H	1913.3 ^H	957.2 ^H	956.1 ^H	847.7 ^H
42	191.8	1794.1 ^H	399.4	658.5	5533.3	1527.1	761.5	765.6	461.6
43	227.8	1777.8	613.9 ^H	760.1	6384.5	1672.9	821.1	851.8	592.6
44	182.2 ^L	1619.6 ^L	376.2 ^L	622.4 ^L	5077.0 ^L	1344.7 ^L	691.4 ^L	653.3 ^L	351.5 ^L
45	224.0	1706.6	573.1	834.2	6782.5	1788.9	914.9	874.0	796.8
N	5	5	5	5	5	5	5	5	5
Mean	213.6	1727.2	503.9	748.4	6351.2	1649.4	829.2	820.2	610.0
S.D.	25.4	69.2	108.3	106.6	1132.3	222.2	108.8	115.3	212.5
S.E.	11.4	30.9	48.4	47.7	506.4	99.4	48.7	51.6	95.0
M.C.									

Animal No.	Adrenal glands (mg)	Adrenal gland (R) (mg)	Adrenal gland (L) (mg)	Ovaries (mg)	Ovary (R) (mg)	Ovary (L) (mg)
41	74.3 ^H	34.6 ^H	39.7 ^H	99.8 ^H	52.2 ^H	47.6
42	56.5	28.2	28.3	68.2	35.4	32.8
43	54.2	27.7	26.5	99.7	44.3	55.4 ^H
44	40.4 ^L	20.9 ^L	19.5 ^L	64.4 ^L	32.7 ^L	31.7 ^L
45	61.1	29.9	31.2	89.9	45.0	44.9
N	5	5	5	5	5	5
Mean	57.3	28.3	29.0	84.4	41.9	42.5
S.D.	12.2	4.9	7.4	17.1	7.9	10.1
S.E.	5.5	2.2	3.3	7.6	3.5	4.5
M.C.						

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons
 B. Bartlett's test
 A. analysis of variance
 K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 7-1-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
46	197.1	1688.9	544.9 ^H	709.9	5688.3	1475.2 ^L	753.4	721.8 ^L	415.8 ^L
47	200.3	1794.7	485.7	691.0 ^L	5365.5 ^L	1625.9	803.5	822.4 ^H	463.3
48	196.6 ^L	1823.4 ^H	355.7	694.4	5800.5	1503.6	739.6 ^L	764.0	449.9
49	239.3 ^H	1789.2	490.5	820.5 ^H	7620.4 ^H	1629.9 ^H	820.3 ^H	809.6	657.8 ^H
50	232.6	1681.3 ^L	334.3 ^L	705.8	6130.0	1518.8	780.4	738.4	525.5
N	5	5	5	5	5	5	5	5	5
Mean	213.2	1755.5	442.2	724.3	6120.9	1550.7	779.4	771.2	502.5
S.D.	21.0	65.6	92.1	54.3	881.6	72.2	33.6	43.8	95.5
S.E.	9.4	29.3	41.2	24.3	394.3	32.3	15.0	19.6	42.7
M.C.									

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Ovaries (mg)	Ovary(R) (mg)	Ovary(L) (mg)
46	50.7	24.6 ^L	26.1	73.3	40.5	32.8
47	55.9	26.7	29.2	82.5	48.4 ^H	34.1
48	49.7 ^L	26.2	23.5 ^L	76.9	33.4	43.5 ^H
49	65.1 ^H	31.8 ^H	33.3 ^H	90.2 ^H	47.3	42.9
50	53.7	28.2	25.5	62.7 ^L	30.8 ^L	31.9 ^L
N	5	5	5	5	5	5
Mean	55.0	27.5	27.5	77.1	40.1	37.0
S.D.	6.1	2.7	3.8	10.3	7.9	5.7
S.E.	2.7	1.2	1.7	4.6	3.6	2.5
M.C.						

*. significantly different from control. p<0.05
 **. significantly different from control. p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons
 B. Bartlett's test
 A. analysis of variance

K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 7-1-2(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of dosing period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
51 (R.T.)									
52 (R.T.)									
53 (R.T.)									
54 (R.T.)									
55 (R.T.)									
56	192.8 ^L	1698.7	462.1	731.2	5915.6	1482.2	721.8 ^L	760.4	433.3
57	201.6	1602.3 ^L	418.8	670.9 ^L	6583.1	1475.4 ^L	742.1	733.3 ^L	387.0
58	198.2	1835.3 ^H	355.6 ^L	740.9	5718.1 ^L	1564.5	781.4	783.1	373.6 ^L
59	234.5 ^H	1791.3	522.2 ^H	936.2 ^H	7625.2 ^H	1750.1 ^H	857.2	892.9 ^H	593.0 ^H
60	227.8	1785.6	475.3	735.6	7133.6	1740.7	861.9 ^H	878.8	474.9
N	5	5	5	5	5	5	5	5	5
Mean	211.0	1742.6	446.8	763.0	6595.1	1602.6	792.9	809.7	452.4
S.D.	18.8	92.8	62.9	100.9	803.4	135.1	64.5	71.9	88.2
S.E.	8.4	41.5	28.1	45.1	359.3	60.4	28.9	32.1	39.4
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	-----

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Ovaries (mg)	Ovary(R) (mg)	Ovary(L) (mg)
51 (R.T.)						
52 (R.T.)						
53 (R.T.)						
54 (R.T.)						
55 (R.T.)						
56	53.7 ^L	26.0 ^L	27.7 ^L	66.5 ^L	34.7 ^L	31.8 ^L
57	60.5	29.4	31.1	92.3	48.0	44.3
58	58.7	30.2	28.5	84.7	38.5	46.2
59	62.1	32.8 ^H	29.3	93.7 ^H	44.2	49.5 ^H
60	65.3 ^H	32.4	32.9 ^H	92.3	51.8 ^H	40.5
N	5	5	5	5	5	5
Mean	60.1	30.2	29.9	85.9	43.4	42.5
S.D.	4.3	2.7	2.1	11.4	6.9	6.8
S.E.	1.9	1.2	0.9	5.1	3.1	3.0
M.C.	-----	-----	-----	-----	-----	-----

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 7-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
1	402.3	1956.6	399.6 ^L	1220.2	12407.3	2458.0 ^L	1215.0 ^L	1243.0 ^L	846.9 ^H
2	405.0	1944.2	718.7 ^H	1270.6	10405.4 ^L	2651.4	1361.4	1290.0	682.5 ^L
3	442.3 ^H	2047.6 ^H	495.9	1297.7 ^H	12973.0 ^H	2999.2	1487.1	1512.1 ^H	740.0
4	412.0	2034.3	643.1	1177.8 ^L	11667.0	2559.3	1298.4	1260.9	706.4
5	391.0 ^L	1900.8 ^L	471.4	1184.2	11705.8	3079.1 ^H	1626.1 ^H	1453.0	802.1
6 (S.S.)									
7 (S.S.)									
8 (S.S.)									
9 (S.S.)									
10 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	410.5	1976.7	545.7	1230.1	11831.7	2749.4	1397.6	1351.8	755.6
S.D.	19.3	62.4	131.1	52.8	963.2	274.7	161.8	122.3	68.0
S.E.	8.6	27.9	58.6	23.6	430.8	122.8	72.4	54.7	30.4

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Testes (mg)	Testis(R) (mg)	Testis(L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
1	53.6	26.3	27.3	3487.6	1615.2	1872.4 ^H	970.2	476.7	493.5
2	50.0 ^L	24.7 ^L	25.3 ^L	3391.9	1706.8	1685.1	1046.4	518.8	527.6
3	60.0 ^H	28.1	31.9 ^H	3597.6 ^H	1828.1 ^H	1769.5	1061.2 ^H	521.1 ^H	540.1 ^H
4	56.9	26.1	30.8	2999.1	1504.7 ^L	1494.4	1031.8	508.8	523.0
5	57.9	28.6 ^H	29.3	2643.4 ^L	1554.2	1089.2 ^L	658.6 ^L	458.6 ^L	200.0 ^L
6 (S.S.)									
7 (S.S.)									
8 (S.S.)									
9 (S.S.)									
10 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	55.7	26.8	28.9	3223.9	1641.8	1582.1	953.6	496.8	456.8
S.D.	3.9	1.6	2.7	395.3	128.6	308.5	168.5	27.8	144.6
S.E.	1.8	0.7	1.2	176.8	57.5	138.0	75.4	12.4	64.7

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S.. scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 7-2-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual males at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
21	433.8	1981.5	485.1	1118.1 ^L	12969.6	2897.6	1458.9	1438.7	755.0 ^L
22	448.1	1973.3 ^L	567.5	1380.2 ^H	13294.3	3011.8 ^H	1505.4 ^H	1506.4 ^H	1037.5 ^H
23	408.7	1988.0	443.2 ^L	1272.6	13098.9	2794.0	1347.7	1446.3	861.0
24	378.8 ^L	2005.4 ^H	512.4	1149.8	10892.4 ^L	2521.0 ^L	1249.7 ^L	1271.3 ^L	809.1
25	452.2 ^H	1986.4	639.8 ^H	1352.3	14349.4 ^H	2972.8	1476.0	1496.8	942.4
26 (S.S.)									
27 (S.S.)									
28 (S.S.)									
29 (S.S.)									
30 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	424.3	1986.9	529.6	1254.6	12920.9	2839.4	1407.5	1431.9	881.0
S.D.	30.6	11.8	76.4	117.5	1257.9	196.4	106.5	94.6	111.5
S.E.	13.7	5.3	34.1	52.6	562.5	87.8	47.6	42.3	49.9
F	2.51	27.90**	2.95	4.96	1.71	1.96	2.31	1.67	2.69
T	0.85	0.36	0.24	0.43	1.54	0.60	0.11	1.16	2.15

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Testes (mg)	Testis(R) (mg)	Testis(L) (mg)	Epididymides (mg)	Epididymis (R) (mg)	Epididymis (L) (mg)
21	47.8 ^L	23.6	24.2 ^L	3061.3 ^L	1525.6 ^L	1535.7 ^L	1064.5	533.5	531.0
22	61.5 ^H	28.7	32.8 ^H	3145.1	1594.3	1550.8	1109.9 ^H	550.4 ^H	559.5
23	58.9	29.9 ^H	29.0	3705.1 ^H	1803.9 ^H	1901.2 ^H	1088.9	531.6	557.3
24	50.1	23.4 ^L	26.7	3155.5	1596.7	1558.8	967.3 ^L	499.9 ^L	467.4 ^L
25	56.2	28.3	27.9	3435.3	1719.1	1716.2	1106.9	544.8	562.1 ^H
26 (S.S.)									
27 (S.S.)									
28 (S.S.)									
29 (S.S.)									
30 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	54.9	26.8	28.1	3300.5	1647.9	1652.5	1067.5	532.0	535.5
S.D.	5.8	3.1	3.2	266.6	111.6	157.1	58.9	19.6	40.1
S.E.	2.6	1.4	1.4	119.2	49.9	70.2	26.3	8.8	17.9
F	2.18	3.70	1.42	2.20	1.33	3.86	8.20*	2.01	13.03*
T	0.25	0.01	0.43	0.36	0.08	0.45	1.43	2.32*	1.17

*. significantly different from control, $p < 0.05$ L, lowest
 **. significantly different from control, $p < 0.01$ H, highest
 S.S., scheduled sacrifice T, Student's t-test or Aspin-Welch's t-test

Appendix 7-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
31	226.4 ^L	1816.9	457.5 ^H	826.1	6378.5 ^L	1866.0 ^H	934.0 ^H	932.0 ^H	601.4 ^H
32	256.0	1816.7	423.5	736.5 ^L	6592.8	1628.0 ^L	823.9 ^L	804.1 ^L	468.8
33	258.4	1931.2 ^H	342.2	805.9	6983.6	1724.3	864.9	859.4	551.4
34	263.2 ^H	1737.4 ^L	412.8	857.7 ^H	7811.7 ^H	1800.2	899.7	900.5	443.8 ^L
35	254.7	1913.3	328.5 ^L	851.1	7240.3	1746.2	894.0	852.2	468.9
36 (S.S.)									
37 (S.S.)									
38 (S.S.)									
39 (S.S.)									
40 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	251.7	1855.1	392.9	815.5	7001.4	1752.9	883.3	869.6	506.9
S.D.	14.5	98.4	55.3	48.7	563.2	88.7	41.3	48.9	66.7
S.E.	6.5	44.0	24.7	21.8	251.9	39.7	18.5	21.8	29.8

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Ovaries (mg)	Ovary(R) (mg)	Ovary(L) (mg)
31	62.1	30.4	31.7	65.7 ^L	37.4 ^L	28.3
32	48.0 ^L	24.5 ^L	23.5 ^L	65.7 ^L	38.3	27.4 ^L
33	71.1 ^H	34.9 ^H	36.2 ^H	95.7	45.9	49.8
34	59.1	27.8	31.3	105.0 ^H	54.5 ^H	50.5 ^H
35	53.6	25.7	27.9	84.7	39.6	45.1
36 (S.S.)						
37 (S.S.)						
38 (S.S.)						
39 (S.S.)						
40 (S.S.)						
N	5	5	5	5	5	5
Mean	58.8	28.7	30.1	83.4	43.1	40.2
S.D.	8.7	4.1	4.7	17.7	7.2	11.5
S.E.	3.9	1.9	2.1	7.9	3.2	5.1

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 7-2-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Absolute organ weights in individual females at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Liver (mg)	Kidneys (mg)	Kidney(R) (mg)	Kidney(L) (mg)	Spleen (mg)
51	262.0 ^H	2010.0 ^H	474.1 ^H	890.1 ^H	7914.5 ^H	2076.6 ^H	1017.1 ^H	1059.5 ^H	663.3 ^H
52	192.1 ^L	1867.4	239.8 ^L	695.7 ^L	5564.4 ^L	1427.1	716.6	710.5	354.2 ^L
53	220.7	1720.1 ^L	397.5	822.4	5827.0	1348.9 ^L	695.7 ^L	653.2 ^L	442.4
54	240.3	1810.1	414.2	889.6	7512.2	1791.6	897.7	893.9	639.8
55	216.1	1790.2	418.8	697.7	6570.0	1641.3	841.1	800.2	417.0
56 (S.S.)									
57 (S.S.)									
58 (S.S.)									
59 (S.S.)									
60 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	226.2	1839.6	388.9	799.1	6677.6	1657.1	833.6	823.5	503.3
S.D.	26.3	108.9	88.2	97.5	1024.8	292.5	132.8	160.4	139.3
S.E.	11.8	48.7	39.4	43.6	458.3	130.8	59.4	71.8	62.3
F	3.29	1.22	2.54	4.00	3.31	10.87*	10.34*	10.79*	4.36
T	1.90	0.24	0.09	0.34	0.62	0.70	0.80	0.62	0.05

Animal No.	Adrenal glands (mg)	Adrenal gland(R) (mg)	Adrenal gland(L) (mg)	Ovaries (mg)	Ovary(R) (mg)	Ovary(L) (mg)
51	74.6 ^H	37.2 ^H	37.4 ^H	108.1 ^H	62.1 ^H	46.0 ^H
52	56.5	27.6	28.9	66.5	35.8	32.7 ^L
53	55.7 ^L	27.3 ^L	28.4 ^L	74.8	40.4	34.4
54	66.0	33.7	32.3	62.0 ^L	26.7 ^L	35.3
55	60.7	31.2	29.5	87.6	45.6	42.0
56 (S.S.)						
57 (S.S.)						
58 (S.S.)						
59 (S.S.)						
60 (S.S.)						
N	5	5	5	5	5	5
Mean	62.7	31.4	31.3	79.8	41.7	38.1
S.D.	7.8	4.2	3.7	18.6	13.4	5.7
S.E.	3.5	1.9	1.7	8.3	6.0	2.5
F	1.25	1.02	1.61	1.11	3.50	4.11
T	0.75	1.04	0.44	0.31	0.21	0.37

*, significantly different from control, p<0.05 L, lowest
 **, significantly different from control, p<0.01 H, highest
 S.S., scheduled sacrifice T, Student's t-test or Aspin-Welch's t-test

Appendix 8-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
1 (R.T.)									
2 (R.T.)									
3 (R.T.)									
4 (R.T.)									
5 (R.T.)									
6	366.2 ^H	5.329	1.969	3.478	31.989 ^H	7.412	3.664	3.747	1.983
7	341.9 ^H	5.324	1.649	3.732	30.436	6.948 ^L	3.491 ^L	3.457 ^L	2.122
8	348.4	5.325	2.028 ^H	3.952 ^H	28.726 ^L	7.517	3.788	3.729	2.364 ^H
9	362.7	5.188 ^L	1.667	3.275 ^L	29.235	7.335	3.772	3.563	1.715 ^L
10	324.3 ^L	6.085 ^H	1.578 ^L	3.655	30.748	8.478 ^H	4.301 ^H	4.177 ^H	2.224
N	5	5	5	5	5	5	5	5	5
Mean	348.7	5.450	1.778	3.618	30.227	7.538	3.803	3.735	2.082
S.D.	16.9	0.360	0.205	0.257	1.290	0.568	0.302	0.275	0.248
S.E.	7.6	0.161	0.092	0.115	0.577	0.254	0.135	0.123	0.111
M.C.	B->A	B->A	B->A	B->A->D	B->A	B->A	B->A	B->A	B->A

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Testes (mg/g)	Testis(R) (mg/g)	Testis(L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
1 (R.T.)									
2 (R.T.)									
3 (R.T.)									
4 (R.T.)									
5 (R.T.)									
6	0.111 ^L	0.054 ^L	0.057 ^L	7.752 ^L	3.839 ^L	3.912 ^L	1.929 ^L	0.989	0.940 ^L
7	0.226 ^H	0.119 ^H	0.107 ^H	8.891	4.375	4.516	2.233	1.099	1.134 ^H
8	0.166	0.080	0.086	10.436 ^H	6.071 ^H	4.365	1.972	1.029	0.943
9	0.163	0.077	0.086	8.755	4.231	4.524	1.981	0.951 ^L	1.030
10	0.184	0.093	0.091	9.580	4.848	4.732 ^H	2.278 ^H	1.170 ^H	1.108
N	5	5	5	5	5	5	5	5	5
Mean	0.170	0.085	0.085	9.083	4.673	4.410	2.079	1.048	1.031
S.D.	0.041	0.024	0.018	0.999	0.861	0.307	0.163	0.088	0.090
S.E.	0.019	0.011	0.008	0.447	0.385	0.137	0.073	0.039	0.040
M.C.	B->K	B->A	B->K	B->A	B->K	B->A	B->A	B->A	B->A

*, significantly different from control. P<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control. P<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

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Appendix 8-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
11	317.4	6.083	1.833	3.498 ^H	30.340	8.543 ^H	4.276 ^H	4.267 ^H	2.181
12	330.8	5.643	2.301 ^H	3.033 ^L	31.015	7.480	3.755	3.725	2.194
13	360.2 ^H	5.660	1.566	3.331	31.232 ^H	6.805 ^L	3.464 ^L	3.341 ^L	1.890
14	294.2 ^L	5.538 ^H	1.842	3.490	29.831	7.440	3.737	3.703	1.631 ^L
15	328.0	5.549 ^L	1.388 ^L	3.328	29.638 ^L	7.300	3.591	3.710	2.339 ^H
N	5	5	5	5	5	5	5	5	5
Mean	326.1	5.895	1.786	3.336	30.411	7.514	3.765	3.749	2.047
S.D.	23.9	0.414	0.345	0.188	0.703	0.635	0.309	0.331	0.284
S.E.	10.7	0.185	0.154	0.084	0.314	0.284	0.138	0.148	0.127
M.C.	-----	-----	-----	1.98	-----	-----	-----	-----	-----

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Testes (mg/g)	Testis (R) (mg/g)	Testis (L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
11	0.132	0.064	0.068	9.008	4.489	4.520	2.159	1.104	1.055
12	0.122 ^L	0.059 ^L	0.063 ^L	8.829	4.409	4.420	2.071	1.018	1.054
13	0.141	0.065	0.076 ^H	7.780 ^L	3.888 ^L	3.893 ^L	1.956 ^L	0.918 ^L	1.038 ^L
14	0.149	0.074	0.075	10.288 ^H	5.143 ^H	5.144 ^H	2.350 ^H	1.212 ^H	1.139 ^H
15	0.157 ^H	0.081 ^H	0.076 ^H	9.463	4.713	4.749	2.165	1.079	1.086
N	5	5	5	5	5	5	5	5	5
Mean	0.140	0.069	0.072	9.074	4.528	4.545	2.140	1.066	1.074
S.D.	0.014	0.009	0.006	0.917	0.458	0.459	0.145	0.109	0.040
S.E.	0.006	0.004	0.003	0.410	0.205	0.205	0.065	0.049	0.018
M.C.	-----	-----	-----	-----	-----	-----	-----	-----	-----

* , significantly different from control, p<0.05
 ** , significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 8-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
16	344.2	5.649	2.527 ^H	3.137	29.758	6.590 ^L	3.241 ^L	3.349 ^L	1.637 ^L
17	312.2 ^L	6.230 ^H	1.905	3.183	30.959	7.275	3.620	3.655	1.722
18	340.1	5.737	1.969	3.669 ^H	31.129	7.495	3.818	3.677	2.015
19	349.5 ^H	5.585 ^L	1.873	3.077	29.115 ^L	7.535	3.774	3.761	2.025
20	324.2	5.624	1.288 ^L	3.049 ^L	31.900 ^H	7.792 ^H	3.821 ^H	3.971 ^H	2.640 ^H
N	5	5	5	5	5	5	5	5	5
Mean	334.0	5.765	1.912	3.223	30.572	7.337	3.655	3.683	2.008
S.D.	15.4	0.266	0.439	0.255	1.119	0.456	0.245	0.224	0.393
S.E.	6.9	0.119	0.197	0.114	0.500	0.204	0.110	0.100	0.176
M.C.				2.77*					

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Testes (mg/g)	Testis(R) (mg/g)	Testis(L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
16	0.142	0.067 ^L	0.075	8.827	4.435	4.392	1.873 ^L	0.969 ^L	0.904 ^L
17	0.145	0.069	0.076	9.183	4.672	4.511	2.181	1.095	1.086 ^H
18	0.152	0.076	0.076	9.082	4.599	4.483	2.163	1.101	1.062
19	0.138 ^L	0.068	0.070 ^L	8.454 ^L	4.207 ^L	4.247 ^L	2.225 ^H	1.144 ^H	1.081
20	0.167 ^H	0.087 ^H	0.080 ^H	9.882 ^H	4.990 ^H	4.892 ^H	2.156	1.077	1.079
N	5	5	5	5	5	5	5	5	5
Mean	0.149	0.073	0.075	9.086	4.581	4.505	2.120	1.077	1.042
S.D.	0.011	0.008	0.004	0.527	0.290	0.240	0.140	0.065	0.078
S.E.	0.005	0.004	0.002	0.236	0.130	0.107	0.063	0.029	0.035
M.C.									

*. significantly different from control. p<0.05
 **. significantly different from control. p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C.. multiple comparisons

B. Bartlett's test

A. analysis of variance

K. Kruskal-Wallis' H test

D. Dunnett's test or Dunnett type mean rank test

Appendix 8-1-1(continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of dosing period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
21 (R.T.)									
22 (R.T.)									
23 (R.T.)									
24 (R.T.)									
25 (R.T.)									
26	324.5	6.004	1.606	3.234	30.421	8.004 ^H	3.967	4.037 ^H	1.876
27	331.5	5.795	2.115 ^H	2.934 ^L	30.917	6.902 ^L	3.368 ^L	3.534 ^L	1.582 ^L
28	338.5 ^H	5.657 ^L	1.525	3.096	34.066 ^H	7.619	3.877	3.742	2.440 ^H
29	297.3 ^L	5.830	1.590	3.372	27.781 ^L	7.552	3.859	3.693	1.894
30	336.7	6.172 ^H	1.456 ^L	3.401 ^H	29.119	7.892	3.972 ^H	3.919	2.206
N	5	5	5	5	5	5	5	5	5
Mean	325.7	5.892	1.658	3.207	30.461	7.594	3.809	3.785	2.000
S.D.	16.8	0.200	0.262	0.195	2.355	0.430	0.252	0.197	0.331
S.E.	7.5	0.089	0.117	0.087	1.053	0.192	0.113	0.088	0.148
M.C.				2.88*					

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Testes (mg/g)	Testis (R) (mg/g)	Testis (L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
21 (R.T.)									
22 (R.T.)									
23 (R.T.)									
24 (R.T.)									
25 (R.T.)									
26	0.176	0.081	0.094 ^H	9.573 ^H	4.800 ^H	4.773 ^H	2.189	1.108	1.080
27	0.183 ^H	0.090 ^H	0.093	8.723 ^L	4.215 ^L	4.508	2.077	1.046	1.031
28	0.164	0.079	0.086	8.898	4.456	4.442 ^L	1.891 ^L	0.930 ^L	0.961 ^L
29	0.146 ^L	0.072 ^L	0.073 ^L	9.090	4.489	4.601	2.248	1.114	1.134 ^H
30	0.178	0.088	0.090	9.007	4.537	4.470	2.295 ^H	1.175 ^H	1.120
N	5	5	5	5	5	5	5	5	5
Mean	0.169	0.082	0.087	9.058	4.499	4.559	2.140	1.075	1.065
S.D.	0.015	0.007	0.009	0.319	0.209	0.134	0.161	0.093	0.071
S.E.	0.007	0.003	0.004	0.143	0.093	0.060	0.072	0.042	0.032
M.C.									

* , significantly different from control, $P < 0.05$
 ** , significantly different from control, $P < 0.01$
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons
 B, Bartlett's test
 A, analysis of variance
 K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 8-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of dosing period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
31 (R.T.)									
32 (R.T.)									
33 (R.T.)									
34 (R.T.)									
35 (R.T.)									
36	208.3	8.462	2.217	3.386 ^L	30.910	8.193	4.019	4.174 ^H	2.485
37	216.0	8.035 ^L	2.149 ^L	3.506	29.231 ^L	7.687 ^L	3.803	3.883 ^L	2.447
38	230.6 ^H	8.288	2.252	3.730	30.111	8.041	3.946	4.095	2.180 ^L
39	201.8 ^L	8.815 ^H	2.157	3.938 ^H	30.944 ^H	8.313 ^H	4.327 ^H	3.986	2.667 ^H
40	216.7	8.482	2.836 ^H	3.410	30.257	7.706	3.756 ^L	3.950	2.409
N	5	5	5	5	5	5	5	5	5
Mean	214.7	8.416	2.322	3.594	30.291	7.988	3.970	4.018	2.438
S.D.	10.8	0.286	0.290	0.235	0.701	0.283	0.226	0.116	0.175
S.E.	4.8	0.128	0.130	0.105	0.314	0.127	0.101	0.052	0.078
M.C.	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->A	B->K

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Ovaries (mg/g)	Ovary (R) (mg/g)	Ovary (L) (mg/g)
31 (R.T.)						
32 (R.T.)						
33 (R.T.)						
34 (R.T.)						
35 (R.T.)						
36	0.272	0.134	0.138	0.349 ^L	0.157 ^L	0.193
37	0.267	0.132	0.135	0.401	0.192	0.209
38	0.317 ^H	0.150	0.167 ^H	0.464 ^H	0.232	0.232 ^H
39	0.258 ^L	0.126 ^L	0.132 ^L	0.433	0.252 ^H	0.180 ^L
40	0.313	0.156 ^H	0.157	0.394	0.199	0.195
N	5	5	5	5	5	5
Mean	0.285	0.140	0.146	0.408	0.206	0.202
S.D.	0.028	0.013	0.015	0.043	0.037	0.020
S.E.	0.012	0.006	0.007	0.019	0.016	0.009
M.C.	B->A	B->A	B->A	B->A	B->A	B->A

*. significantly different from control, p<0.05 L. lowest M.C., multiple comparisons
 **. significantly different from control, p<0.01 H. highest B. Bartlett's test K. Kruskal-Wallis' H test
 R.T., for recovery test A. analysis of variance D. Dunnett's test or Dunnett type mean rank test

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Appendix 8-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of dosing period; the dosage of 5 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
41	242.2 ^H	7.175 ^L	2.299	3.578	32.943 ^H	7.900	3.952	3.948	3.500
42	191.8	9.354 ^H	2.082	3.433	28.849	7.962	3.970	3.992 ^H	2.407
43	227.8	7.804	2.695 ^H	3.337 ^L	28.027	7.344 ^L	3.604 ^L	3.739	2.601
44	182.2 ^L	8.889	2.065 ^L	3.416	27.865 ^L	7.380	3.795	3.586 ^L	1.929 ^L
45	224.0	7.619	2.558	3.724 ^H	30.279	7.986 ^H	4.084 ^H	3.902	3.557 ^H
N	5	5	5	5	5	5	5	5	5
Mean	213.6	8.168	2.340	3.498	29.593	7.714	3.881	3.833	2.799
S.D.	25.4	0.915	0.282	0.154	2.103	0.323	0.186	0.168	0.710
S.E.	11.4	0.409	0.126	0.069	0.940	0.145	0.083	0.075	0.317
M.C.									

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Ovaries (mg/g)	Ovary (R) (mg/g)	Ovary (L) (mg/g)
41	0.307 ^H	0.143	0.164 ^H	0.412	0.216 ^H	0.197
42	0.295	0.147 ^H	0.148	0.356	0.185	0.171 ^L
43	0.238	0.122	0.116	0.438 ^H	0.194	0.243 ^H
44	0.222 ^L	0.115 ^L	0.107 ^L	0.353 ^L	0.179 ^L	0.174
45	0.273	0.133	0.139	0.401	0.201	0.200
N	5	5	5	5	5	5
Mean	0.267	0.132	0.135	0.392	0.195	0.197
S.D.	0.036	0.014	0.023	0.037	0.014	0.029
S.E.	0.016	0.006	0.010	0.016	0.006	0.013
M.C.						

*, significantly different from control, p<0.05
 **, significantly different from control, p<0.01
 R.T., for recovery test

L, lowest
 H, highest

M.C., multiple comparisons

B, Bartlett's test
 A, analysis of variance

K, Kruskal-Wallis' H test
 D, Dunnett's test or Dunnett type mean rank test

Appendix 8-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of dosing period; the dosage of 10 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
46	197.1	8.569	2.765 ^H	3.602 ^H	28.860	7.485	3.822	3.662	2.110 ^L
47	200.3	8.960	2.425	3.450	26.787	8.117 ^H	4.011 ^H	4.106 ^H	2.313
48	196.6 ^L	9.275 ^H	1.809	3.532	29.504	7.648	3.762	3.886	2.288
49	239.3 ^H	7.477	2.050	3.429	31.845 ^H	6.811	3.428	3.383	2.749 ^H
50	232.6	7.228 ^L	1.437 ^L	3.034 ^L	26.354 ^L	6.530 ^L	3.355 ^L	3.175 ^L	2.259
N	5	5	5	5	5	5	5	5	5
Mean	213.2	8.302	2.097	3.409	28.670	7.318	3.676	3.642	2.344
S.D.	21.0	0.906	0.518	0.221	2.220	0.643	0.276	0.374	0.240
S.E.	9.4	0.405	0.232	0.099	0.993	0.288	0.124	0.167	0.107
M.C.									

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Ovaries (mg/g)	Ovary(R) (mg/g)	Ovary(L) (mg/g)
46	0.257	0.125	0.132	0.372	0.205	0.166
47	0.279 ^H	0.133 ^H	0.146 ^H	0.412 ^H	0.242 ^H	0.170
48	0.253	0.133 ^H	0.120	0.391	0.170	0.221 ^H
49	0.272	0.133 ^H	0.139	0.377	0.198	0.175
50	0.231 ^L	0.121 ^L	0.110 ^L	0.270 ^L	0.132 ^L	0.137 ^L
N	5	5	5	5	5	5
Mean	0.258	0.129	0.129	0.364	0.189	0.175
S.D.	0.019	0.006	0.014	0.055	0.041	0.030
S.E.	0.008	0.003	0.006	0.025	0.018	0.014
M.C.						

*, significantly different from control, p<0.05 L, lowest M.C., multiple comparisons
 **, significantly different from control, p<0.01 H, highest B, Bartlett's test K, Kruskal-Wallis' H test
 R.T., for recovery test A, analysis of variance D, Dunnett's test or Dunnett type mean rank test

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Appendix 8-1-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of dosing period; the dosage 20 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
51 (R.T.)									
52 (R.T.)									
53 (R.T.)									
54 (R.T.)									
55 (R.T.)									
56	192.8 ^L	8.811	2.397 ^H	3.793	30.683	7.688	3.744	3.944	2.247
57	201.6	7.948	2.077	3.328	32.654 ^H	7.318 ^L	3.681	3.637 ^L	1.920
58	198.2	9.260 ^H	1.794 ^L	3.738	28.850 ^L	7.894 ^H	3.942 ^H	3.951 ^H	1.885 ^L
59	234.5 ^H	7.639 ^L	2.227	3.992 ^H	32.517	7.463	3.655 ^L	3.808	2.529 ^H
60	227.8	7.838	2.086	3.229 ^L	31.315	7.641	3.784	3.858	2.085
N	5	5	5	5	5	5	5	5	5
Mean	211.0	8.299	2.116	3.616	31.204	7.601	3.761	3.840	2.133
S.D.	18.8	0.699	0.222	0.324	1.553	0.220	0.113	0.128	0.264
S.E.	8.4	0.313	0.099	0.145	0.695	0.099	0.051	0.057	0.118
M.C.									

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Ovaries (mg/g)	Ovary (R) (mg/g)	Ovary (L) (mg/g)
51 (R.T.)						
52 (R.T.)						
53 (R.T.)						
54 (R.T.)						
55 (R.T.)						
56	0.279	0.135 ^L	0.144	0.345 ^L	0.180 ^L	0.165 ^L
57	0.300 ^H	0.146	0.154 ^H	0.458 ^H	0.238 ^H	0.220
58	0.296	0.152 ^H	0.144	0.427	0.194	0.233 ^H
59	0.265 ^L	0.140	0.125 ^L	0.400	0.188	0.211
60	0.287	0.142	0.144	0.405	0.227	0.178
N	5	5	5	5	5	5
Mean	0.285	0.143	0.142	0.407	0.205	0.201
S.D.	0.014	0.006	0.011	0.042	0.026	0.029
S.E.	0.006	0.003	0.005	0.019	0.011	0.013
M.C.						

*. significantly different from control, p<0.05
 **. significantly different from control, p<0.01
 R.T., for recovery test

L. lowest
 H. highest

M.C., multiple comparisons
 B. Bartlett's test
 A. analysis of variance

K. Kruskal-Wallis' H test
 D. Dunnett's test or Dunnett type mean rank test

Appendix 8-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
1	402.3	4.864	0.993 ^L	3.033	30.841 ^H	6.110 ^L	3.020 ^L	3.090	2.105 ^H
2	405.0	4.800	1.775 ^H	3.137 ^H	25.692 ^L	6.547	3.361	3.185	1.685
3	442.3 ^H	4.629 ^L	1.121	2.934	29.331	6.781	3.362	3.419	1.673 ^L
4	412.0	4.938 ^H	1.561	2.859 ^L	28.318	6.212	3.151	3.060 ^L	1.715
5	391.0 ^L	4.861	1.206	3.029	29.938	7.875 ^H	4.159 ^H	3.716 ^H	2.051
6 (S.S.)									
7 (S.S.)									
8 (S.S.)									
9 (S.S.)									
10 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	410.5	4.818	1.331	2.998	28.824	6.705	3.411	3.294	1.846
S.D.	19.3	0.117	0.326	0.106	1.977	0.707	0.443	0.275	0.213
S.E.	8.6	0.052	0.146	0.047	0.884	0.316	0.198	0.123	0.095

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Testes (mg/g)	Testis(R) (mg/g)	Testis(L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
1	0.133	0.065	0.068	8.669 ^H	4.015	4.654 ^H	2.412	1.185	1.227
2	0.123 ^L	0.061 ^L	0.062 ^L	8.375	4.214 ^H	4.161	2.584 ^H	1.281 ^H	1.303 ^H
3	0.136	0.064	0.072	8.134	4.133	4.001	2.399	1.178	1.221
4	0.138	0.063	0.075 ^H	7.279	3.652 ^L	3.627	2.504	1.235	1.269
5	0.148 ^H	0.073 ^H	0.075 ^H	6.761 ^L	3.975	2.786 ^L	1.684 ^L	1.173 ^L	0.512 ^L
6 (S.S.)									
7 (S.S.)									
8 (S.S.)									
9 (S.S.)									
10 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	0.136	0.065	0.070	7.844	3.998	3.846	2.317	1.210	1.106
S.D.	0.009	0.005	0.006	0.797	0.215	0.698	0.361	0.047	0.334
S.E.	0.004	0.002	0.002	0.356	0.096	0.312	0.162	0.021	0.149

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 8-2-1 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual males at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
21	433.8	4.568	1.118	2.577 ^L	29.898	6.680	3.363 ^H	3.317	1.740 ^L
22	448.1	4.404	1.266	3.080	29.668	6.721	3.360	3.362	2.315 ^H
23	408.7	4.864	1.084 ^L	3.114 ^H	32.050 ^H	6.836 ^H	3.298	3.539 ^H	2.107
24	378.8 ^L	5.294 ^H	1.353	3.035	28.755 ^L	6.655	3.299	3.356	2.136
25	452.2 ^H	4.393 ^L	1.415 ^H	2.990	31.732	6.574 ^L	3.264 ^L	3.310 ^L	2.084
26 (S.S.)									
27 (S.S.)									
28 (S.S.)									
29 (S.S.)									
30 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	424.3	4.705	1.247	2.959	30.421	6.693	3.317	3.377	2.076
S.D.	30.6	0.380	0.144	0.219	1.413	0.096	0.043	0.094	0.209
S.E.	13.7	0.170	0.064	0.098	0.632	0.043	0.019	0.042	0.093
F	2.51	10.64*	5.11	4.26	1.96	53.96**	105.23**	8.63*	1.04
T	0.85	0.64	0.53	0.36	1.47	0.04	0.47	0.64	1.73

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Testes (mg/g)	Testis(R) (mg/g)	Testis(L) (mg/g)	Epididymides (mg/g)	Epididymis (R) (mg/g)	Epididymis (L) (mg/g)
21	0.110 ^L	0.054 ^L	0.056 ^L	7.057	3.517 ^L	3.540	2.454	1.230	1.224 ^L
22	0.137	0.064	0.073 ^H	7.019 ^L	3.558	3.461 ^L	2.477	1.228	1.249
23	0.144 ^H	0.073 ^H	0.071	9.066 ^H	4.414 ^H	4.652 ^H	2.664 ^H	1.301	1.364 ^H
24	0.132	0.062	0.070	8.330	4.215	4.115	2.554	1.320 ^H	1.234
25	0.124	0.063	0.062	7.597	3.802	3.795	2.448 ^L	1.205 ^L	1.243
26 (S.S.)									
27 (S.S.)									
28 (S.S.)									
29 (S.S.)									
30 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	0.129	0.063	0.066	7.814	3.901	3.913	2.519	1.257	1.263
S.D.	0.013	0.007	0.007	0.878	0.399	0.486	0.091	0.050	0.057
S.E.	0.006	0.003	0.003	0.393	0.178	0.217	0.041	0.023	0.026
F	2.10	2.16	1.69	1.22	3.43	2.06	15.71*	1.17	33.90**
T	0.87	0.55	0.99	0.06	0.48	0.18	1.22	1.51	1.03

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 8-2-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of recovery period; the dosage of 0 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney(R) (mg/g)	Kidney(L) (mg/g)	Spleen (mg/g)
31	226.4 ^L	8.025 ^H	2.021 ^H	3.649 ^H	28.174	8.242 ^H	4.125 ^H	4.117 ^H	2.656 ^H
32	256.0	7.096	1.654	2.877 ^L	25.753 ^L	6.359 ^L	3.218 ^L	3.141 ^L	1.831
33	258.4	7.706	1.324	3.119	27.026	6.673	3.347	3.326	2.134
34	263.2 ^H	6.601 ^L	1.568	3.259	29.680 ^H	6.840	3.418	3.421	1.686 ^L
35	254.7	7.512	1.290 ^L	3.342	28.427	6.856	3.510	3.346	1.841
36 (S.S.)									
37 (S.S.)									
38 (S.S.)									
39 (S.S.)									
40 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	251.7	7.388	1.571	3.249	27.812	6.994	3.524	3.470	2.030
S.D.	14.5	0.554	0.296	0.285	1.488	0.726	0.353	0.376	0.386
S.E.	6.5	0.248	0.132	0.127	0.665	0.325	0.158	0.168	0.173

Animal No.	Adrenal glands (mg/g)	Adrenal gland(R) (mg/g)	Adrenal gland(L) (mg/g)	Ovaries (mg/g)	Ovary(R) (mg/g)	Ovary(L) (mg/g)
31	0.274	0.134	0.140 ^H	0.290	0.165	0.125
32	0.188 ^L	0.096 ^L	0.092 ^L	0.257 ^L	0.150 ^L	0.107 ^L
33	0.275 ^H	0.135 ^H	0.140 ^H	0.370	0.178	0.193 ^H
34	0.225	0.106	0.119	0.399 ^H	0.207 ^H	0.192
35	0.210	0.101	0.110	0.333	0.155	0.177
36 (S.S.)						
37 (S.S.)						
38 (S.S.)						
39 (S.S.)						
40 (S.S.)						
N	5	5	5	5	5	5
Mean	0.234	0.114	0.120	0.330	0.171	0.159
S.D.	0.039	0.019	0.021	0.058	0.023	0.040
S.E.	0.017	0.008	0.009	0.026	0.010	0.018

*. significantly different from control, p<0.05 L. lowest
 **. significantly different from control, p<0.01 H. highest
 S.S.. scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 8-2-2 (continued)

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Relative organ weights in individual females at the end of recovery period; the dosage of 20 mg/kg

Animal No.	Body weight (g)	Brain (mg/g)	Thymus (mg/g)	Heart (mg/g)	Liver (mg/g)	Kidneys (mg/g)	Kidney (R) (mg/g)	Kidney (L) (mg/g)	Spleen (mg/g)
51	262.0 ^H	7.672	1.810	3.397	30.208	7.926 ^H	3.882	4.044 ^H	2.532
52	192.1 ^L	9.721 ^H	1.248 ^L	3.622	28.966	7.429	3.730	3.699	1.844 ^L
53	220.7	7.794	1.801	3.726 ^H	26.402 ^L	6.112 ^L	3.152 ^L	2.960 ^L	2.005
53	240.3	7.533 ^L	1.724	3.702	31.262 ^H	7.456	3.736	3.720	2.663 ^H
55	216.1	8.284	1.938 ^H	3.229 ^L	30.403	7.595	3.892 ^H	3.703	1.930
56 (S.S.)									
57 (S.S.)									
58 (S.S.)									
59 (S.S.)									
60 (S.S.)									
N	5	5	5	5	5	5	5	5	5
Mean	226.2	8.201	1.704	3.535	29.448	7.304	3.678	3.625	2.195
S.D.	26.3	0.896	0.266	0.215	1.890	0.695	0.304	0.399	0.375
S.E.	11.8	0.401	0.119	0.096	0.845	0.311	0.136	0.179	0.168
F	3.29	2.62	1.23	1.76	1.61	1.09	1.34	1.13	1.06
T	1.90	1.73	0.75	1.79	1.52	0.69	0.74	0.63	0.69

Animal No.	Adrenal glands (mg/g)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg/g)	Ovaries (mg/g)	Ovary (R) (mg/g)	Ovary (L) (mg/g)
51	0.285	0.142	0.143	0.413 ^H	0.237 ^H	0.176
52	0.294 ^H	0.144 ^H	0.150 ^H	0.346	0.176	0.170
53	0.252 ^L	0.124 ^L	0.129 ^L	0.339	0.183	0.156
53	0.275	0.140	0.134	0.258 ^L	0.111 ^L	0.147 ^L
55	0.281	0.144 ^H	0.137	0.405	0.211	0.194 ^H
56 (S.S.)						
57 (S.S.)						
58 (S.S.)						
59 (S.S.)						
60 (S.S.)						
N	5	5	5	5	5	5
Mean	0.277	0.139	0.139	0.352	0.184	0.169
S.D.	0.016	0.008	0.008	0.062	0.047	0.018
S.E.	0.007	0.004	0.004	0.028	0.021	0.008
F	6.07	4.91	6.35	1.17	4.30	4.84
T	2.29	2.66*	1.86	0.59	0.54	0.50

*. significantly different from control. p<0.05 L, lowest
 **. significantly different from control. p<0.01 H, highest
 S.S., scheduled sacrifice T. Student's t-test or Aspin-Welch's t-test

Appendix 9-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in individual males at the end of dosing period

Dose	0 mg/kg					5 mg/kg					10 mg/kg					20 mg/kg				
Animal No.	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	26	27	28	29	30
(Eye)																				
Area, dark	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-

-, negative; +, positive.

Appendix 9-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in individual females at the end of dosing period

Dose	0 mg/kg					5 mg/kg					10 mg/kg					20 mg/kg				
Animal No.	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	56	57	58	59	60
(Kidney)																				
Cyst	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(Spleen)																				
Small	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-

-, negative; +, positive.

Appendix 9-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Macroscopical findings in individual males at the end of recovery period

Dose	0 mg/kg					20 mg/kg				
Animal No.	1	2	3	4	5	21	22	23	24	25
(Kidney)										
Enlargement	-	-	-	-	-	-	-	+	-	-
Area, pale, cortex	-	-	-	-	-	-	-	+	-	-
(Testis)										
Small, unilateral	-	-	-	-	+	-	-	-	-	-
(Epididymis)										
Small, unilateral	-	-	-	-	+	-	-	-	-	-

-, negative; +, positive.

Appendix 10-1-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in individual males at the end of dosing period

Dose Animal No.	0 mg/kg					5 mg/kg					10 mg/kg					20 mg/kg				
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	26	27	28	29	30
(Kidney)																				
Eosinophilic body, proximal tubule	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-
Basophilic tubule	±	±	±	-	±	-	±	±	±	-	±	±	±	+	±	-	-	±	±	±
Cellular infiltration, lymphocyte	±	±	±	±	±	-	±	±	±	-	±	±	±	±	±	±	±	±	-	±
Cast, proteinous	-	±	-	-	±	-	-	-	-	-	-	-	-	±	-	+	-	-	-	-
(Spleen)																				
Deposit, pigment, brown	+	+	+	+	+											+	+	+	+	+
Hematopoiesis, extramedullary	+	±	±	+	±											±	±	++	±	±
(Heart)																				
Myocardial degeneration / fibrosis	-	±	-	-	-											-	-	-	+	-
(Liver)																				
Abnormality	-	-	-	-	-											-	-	-	-	-
(Adrenal gland)																				
Abnormality	-	-	-	-	-											-	-	-	-	-
(Stomach)																				
Abnormality	-	-	-	-	-											-	-	-	-	-
(Testis)																				
Abnormality	-	-	-	-	-											-	-	-	-	-
(Epididymis)																				
Abnormality	-	-	-	-	-											-	-	-	-	-
(Eye)																				
Hemorrhage, vitreous cavity																				+

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe.

Appendix 10-1-2

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in individual females at the end of dosing period

Dose Animal No.	0 mg/kg					20 mg/kg				
	36	37	38	39	40	56	57	58	59	60
(Kidney)										
Basophilic tubule	±	±	-	-	±	-	-	±	±	-
Cellular infiltration, lymphocyte	±	±	-	-	-	-	-	±	±	-
Cyst, cortex	+	-	-	-	-	-	-	-	-	-
(Spleen)										
Deposit, pigment, brown	+	+	+	+	+	+	+	+	+	+
Hematopoiesis, extramedullary	±	±	±	±	±	±	±	-	+	±
(Heart)										
Abnormality	-	-	-	-	-	-	-	-	-	-
(Liver)										
Abnormality	-	-	-	-	-	-	-	-	-	-
(Adrenal gland)										
Abnormality	-	-	-	-	-	-	-	-	-	-
(Stomach)										
Abnormality	-	-	-	-	-	-	-	-	-	-
(Ovary)										
Abnormality	-	-	-	-	-	-	-	-	-	-

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe.

Appendix 10-2-1

Twenty-eight-day repeat dose oral toxicity study with subsequent 14-day recovery test of TMAH in rats

Histological findings in individual males at the end of recovery period

Dose	0 mg/kg					20 mg/kg				
	1	2	3	4	5	21	22	23	24	25
Animal No.										
(Kidney)										
Eosinophilic body, proximal tubule	+	-	-	-	+	-	-	±	+	±
Basophilic tubule	±	±	±	-	±	±	±	±	±	±
Cellular infiltration, lymphocyte	±	±	±	±	±	±	±	±	±	±
(Testis)										
Atrophy, seminiferous tubule, unilateral					+++					
(Epididymis)										
Decrease, sperm, unilateral					+++					

-, negative; ±, very slight; +, slight; ++, moderate; +++, severe.



Photo A microphotograph of the kidney from the male animal of TMAH, 20 mg/kg group (Animal No. 26) showing eosinophilic body in proximal tubule, H-E, x350.

ほ乳類を用いる28日間の反復投与毒性試験結果報告書

1. 一般的事項

化学物質の名称 (IUPAC 命名法による)	N,N,N-トリメチルメタンアミンヒドロキシド				
別名	水酸化テトラメチルアンモニウム	物理化学的性状	分子量	91.03	
化学式： (CH ₃) ₄ NOH			常温における性状	水溶液	
			安定性	安定	
			融点	提供元資料に記載なし	
			沸点	提供元資料に記載なし	
			蒸気圧	提供元資料に記載なし	
			分配係数	提供元資料に記載なし	
			溶解性	提供元資料に記載なし	
			溶解度		水
DMSO	提供元資料に記載なし				
アセトン	提供元資料に記載なし				
その他 ()	提供元資料に記載なし				
純度	20.19 wt% (水溶液)				
不純物	炭酸根 3 ppm 塩化物 0.17 ppm				

2. 投与量設定試験

試験 No.	試験の種類 及び期間	動物種	1群 当たりの 動物数	投与 経路	投与量 (mg/kg)	一般状態等	実験場所
1	投与量設定 試験 7日間	ラット	雄：3 雌：3	経口	0 mg/kg 1 mg/kg 5 mg/kg 10 mg/kg	異常なし 異常なし 異常なし 異常なし	財食品薬品安全センター 秦野研究所
2	投与量設定 試験 5日間	ラット	雄：3 雌：3	経口	20 mg/kg	剖検：腺胃粘膜の肥厚 (雄1例)	
3	急性経口投与 毒性予備 試験 1回投与 7日間観察	ラット	雄：3 雌：3	経口	25 mg/kg 50 mg/kg および 100 mg/kg	一般状態：半眼、自発運動の減少等 体重：体重減少または増加抑制 } 間代性あるいは間代性-強直性痙攣 等発症の後に全例死亡	

3-1 . 28日間反復投与毒性試験

被験物質投与期間		自1999年2月25日				至1999年3月24日					
使用動物・系統		ラット, Sprague-Dawley, SPF				動物数 対照、高用量 : 雌雄各10匹 低用量、中用量 : 雌雄各5匹					
投与経路		強制経口投与				動物数 対照、高用量 : 雌雄各5匹					
群 投与量 (mg/kg) 性		対照 0		低用量 5		中用量 10		高用量 20		回復群 0 20	
		雄	雌	雄	雌	雄	雌	雄	雌	雄	雌
死亡例数		-	-	-	-	-	-	-	-	-	-
体重				-	-	-	-	-	-	-	-
摂餌量	投与第1週 投与第2週 投与第3週 投与第4週 回復第1週 回復第2週			-	-	▽	-	▼	▼		
一般状態	投与直後の流涎 (投与後1時間以内に消失) 投与直後の流涎 (投与後1時間以上継続) 投与1時間後の流涎 眼球の暗色化 (片側)	-	-	1	-	4	5	8	9		
尿検査 (投与第26日および 回復第12日に検査)	pH (6.5)	-	1	-	-	-	-	-	2	-	-
	(7.0)	3	6	1	2	-	1	3	2	-	3
	(7.5)	4	3	1	1	2	3	3	4	2	-
	(8.0)	1	-	2	-	2	1	-	2	2	-
	(8.5)	1	-	1	1	1	-	1	-	1	1
	(≥9.0)	1	-	1	1	-	-	3	-	1	1
	蛋白 (±)	2	5	1	-	2	-	-	-	1	1
	(+)	8	-	4	-	3	-	10	-	3	4
	ケトン体 (±)	5	1	4	-	3	-	6	1	3	-
	(+)	1	-	-	-	1	-	2	-	1	1
潜血 (±)	-	-	-	-	-	-	-	-	-	-	
(+)	-	-	-	-	1	-	-	-	-	-	
ウロビリノーゲン (±)	10	9	5	5	5	5	9	8	5	5	
(+)	-	1	-	-	-	-	1	2	-	-	
ナトリウム排泄量				-	-	-	-	-	-	△	△
カリウム排泄量				-	-	-	-	-	-	△	△
塩素排泄量				-	-	-	-	-	-	△	△
血液学検査	赤血球数			-	-	-	-	-	-	▽	▽
	血色素量			-	-	-	-	-	-	-	▽
	平均赤血球容積			-	-	-	-	-	-	▲	-
	平均赤血球血色素量			-	-	-	-	-	-	▲	-
	網状赤血球比率			-	-	-	-	-	-	△	-
	血小板数			-	-	-	-	-	-	▽	-
	プロトロンビン時間			-	-	-	-	▽	-	-	-
	活性部分トロンボプラスチン時間			-	-	-	-	-	-	-	▽
生化学検査	総蛋白濃度			-	-	-	-	-	-	▼	-
器官重量 (絶対重量)	心臓			▽	-	▼	-	▼	-	-	-
器官重量 (相対重量)	解剖時体重			-	-	-	-	-	-	-	-
	心臓			-	-	▽	-	▽	-	-	-

注) △, 対照群に比べ有意な増加 (p<0.05)
▽, 対照群に比べ有意な減少 (p<0.05)
↑, 対照群に比べ増加傾向
数値, 例数

▲, 対照群に比べ有意な増加 (p<0.01)
▼, 対照群に比べ有意な減少 (p<0.01)
-, 変化なし; ±~+, 陽性

