NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of

Triethanolamine (CAS No. 102-71-6) in B6C3F$_1$ Mice (Dermal Study)

NTP TR 518

MAY 2004

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TRIETHANOLAMINE

(CAS NO. 102-71-6)

IN B6C3F$_1$ MICE

(DERMAL STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

May 2004

NTP TR 518

NIH Publication No. 04-4452

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Perspectives (EHP) http://ehp.niehs.nih.gov (866-541-3841 or 919-653-2590). In addition, printed copies of these reports are available from EHP as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears at the end of this Technical Report.

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CONTENTS

ABSTRACT 5

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 8

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 9

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 10

INTRODUCTION 11

MATERIALS AND METHODS 19

RESULTS 27

DISCUSSION AND CONCLUSIONS 39

REFERENCES 43

APPENDIX A Summary of Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine 49

APPENDIX B Summary of Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine 87

APPENDIX C Genetic Toxicology 125

APPENDIX D Chemical Characterization and Dose Formulation Studies 135

APPENDIX E Ingredients, Nutrient Composition, and Contaminant Levels in NTP-2000 Rat and Mouse Ration 145

APPENDIX F Sentinel Animal Program 149

APPENDIX G Absorption, Distribution, Metabolism, and Excretion Studies 151

SUMMARY

Background

Triethanolamine is used to make many products, including household detergents and polishes, herbicides, vegetable and mineral oils, paraffin and waxes, plastics, resins, adhesives, and ointments. We studied the effects of triethanolamine on male and female mice to identify potential toxic or cancer-related hazards to humans.

Methods

We placed solutions of triethanolamine dissolved in acetone onto the shaved skin on the backs of male and female mice 5 days per week for 2 years. Male mice received concentrations of 200, 630, or 2,000 milligrams of triethanolamine per kilogram of body weight, and female mice received half those concentrations. Control groups received only acetone.

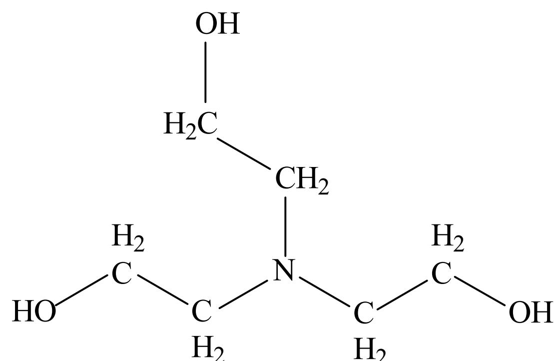
Results

The dosed animals did not have higher death rates than the control animals. The male mice receiving 2,000 mg triethanolamine per kg body weight weighed less than the male control animals. There was a slight increase in hemangiosarcomas (tumors of the vascular system) in the livers of males exposed to triethanolamine. In female mice exposed to triethanolamine, there was a significant increase in liver tumors.

Conclusions

We conclude that triethanolamine caused liver tumors in female mice and may have caused a slight increase in hemangiosarcomas of the liver in male mice.

ABSTRACT



TRIETHANOLAMINE

CAS No. 102-71-6

Chemical Formula: $C_6H_{15}NO_3$ Molecular Weight: 149.19

Synonyms: Nitrilo-2,2′,2′′-triethanol; 2,2′,2′′-nitrilotriethanol; 2,2′,2′′-nitrilotrisethanol; TEA; triaethanolamin-NG; triethanolamin; triethylolamine; tri(hydroxyethyl)amine; 2,2′,2′′-trihydroxytriethylamine; trihydroxytriethylamine; tris(hydroxyethyl)amine; tris(2-hydroxyethyl)amine; trolamine

Trade names: Daltogen, Sterolamide, Thiofaco T-35

Triethanolamine is widely used in the manufacturing of household detergents and polishes, textiles, agricultural herbicides, mineral and vegetable oils, paraffin and waxes, pharmaceutical ointments, petroleum demulsifiers, synthetic resins, plasticizers, adhesives, and sealants. It is used as a chemical intermediate for anionic and nonionic surfactants, a vulcanization accelerator, a humectant and softening agent and in many other industrial applications. The National Cancer Institute nominated triethanolamine for study because of its widespread use in cosmetics and other consumer products, its high potential for worker exposure due to its many industrial uses, and its potential for conversion to the carcinogen *N*-nitrosodiethanolamine. Previous 3-month and 2-year studies of triethanolamine were conducted by the National Toxicology Program in F344/N rats and $B6C3F_1$ mice; results from the 2-year rat study indicated *equivocal evidence of carcinogenic activity* based on a marginal increase in the incidence of renal tubule adenoma (NTP, 1991). Interpretation of the results from the 2-year study in mice was complicated by *Helicobacter hepaticus* infection, prompting a repeat 2-year study in mice. Male and female $B6C3F_1$ mice received triethanolamine (greater than 99% pure) by dermal application for 2 years; a study of absorption, distribution, metabolism, and excretion was performed in additional mice. Genetic toxicology studies were conducted in *Salmonella typhimurium,* cultured Chinese hamster ovary cells, *Drosophila melanogaster,* and mouse peripheral blood erythrocytes.

2-YEAR STUDY

Groups of 50 male and 50 female mice received dermal applications of 0, 200, 630, or 2,000 mg/kg (males) and 0, 100, 300, or 1,000 mg/kg (females) triethanolamine in

acetone, 5 days per week, for 104 (males) or 104 to 105 (females) weeks.

Survival of all dosed groups was similar to that of the vehicle control groups. Body weights of 2,000 mg/kg males were less than those of the vehicle controls from weeks 17 to 37 and at the end of the study; body weights of dosed groups of females were similar to those of the vehicle controls throughout the study. Treatment-related clinical findings included skin irritation at the site of application, which increased with increasing dose and was more severe in males than in females.

Gross lesions observed at necropsy included nodules and masses of the liver in dosed females. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all dosed groups of females. The incidence of hemangiosarcoma of the liver in 630 mg/kg males was marginally increased. The incidences of eosinophilic focus in all dosed groups of mice were greater than those in the vehicle controls.

Gross lesions observed at necropsy included visible crusts at the site of application in all dosed groups of mice. Treatment-related epidermal hyperplasia, suppurative inflammation, ulceration, and dermal chronic inflammation occurred at the site of application in most dosed groups of mice, and the incidences and severities of these lesions generally increased with increasing dose.

Genetic Toxicology

Triethanolamine was not mutagenic in any of the *in vitro* or *in vivo* tests. It did not induce mutations in *Salmonella typhimurium*, and no induction of sister chromatid exchanges or chromosomal aberrations was noted in cultured Chinese hamster ovary cells exposed to triethanolamine. These *in vitro* tests were all conducted with and without S9 metabolic activation. Triethanolamine did not induce sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* exposed by feeding or injection. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples of male or female mice that received dermal applications of triethanolamine for 13 weeks.

Conclusions

Under the conditions of this 2-year dermal study, there was *equivocal evidence of carcinogenic activity** of triethanolamine in male $B6C3F_1$ mice based on the occurrence of liver hemangiosarcoma. There was *some evidence of carcinogenic activity* in female $B6C3F_1$ mice based on increased incidences of hepatocellular adenoma.

Exposure to triethanolamine by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related nonneoplastic lesions at the site of application.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Triethanolamine

	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses in acetone by dermal application	Vehicle control, 200, 630, or 2,000 mg/kg	Vehicle control, 100, 300, or 1,000 mg/kg
Survival rates	37/50, 43/50, 34/50, 40/50	35/50, 34/50, 41/50, 32/50
Body weights	2,000 mg/kg group less than the vehicle control group	Dosed groups similar to the vehicle control group
Nonneoplastic effects	Liver: eosinophilic focus (9/50, 20/50, 31/50, 30/50) Skin (site of application): epidermis, hyperplasia (5/50, 44/50, 45/50, 49/50); epidermis, inflammation, suppurative (1/50, 11/50, 33/50, 42/50); epidermis, ulcer (0/50, 3/50, 20/50, 47/50); dermis, inflammation, chronic (1/50, 15/50, 40/50, 49/50)	Liver: eosinophilic focus (16/50, 22/50, 28/50, 32/50) Skin (site of application): epidermis, hyperplasia (14/50, 50/50, 46/50, 50/50); epidermis, inflammation, suppurative (1/50, 2/50, 20/50, 32/50); epidermis, ulcer (1/50, 1/50, 6/50, 17/50); dermis, inflammation, chronic (4/50, 27/50, 31/50, 44/50)
Neoplastic effects	None	Liver: hepatocellular adenoma (9/50, 18/50, 20/50, 33/50); hepatocellular adenoma or carcinoma (12/50, 23/50, 24/50, 34/50)
Equivocal findings	Liver: hemangiosarcoma (1/50, 0/50, 6/50, 1/50)	
Level of evidence of carcinogenic activity	Equivocal evidence	Some evidence

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro:*	Negative with and without S9
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro:*	Negative with and without S9
Sex-linked recessive lethal mutations *Drosophila melanogaster:*	Negative when administered in feed or by injection
Micronucleated erythrocytes Mouse peripheral blood *in vivo:*	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results **(clear evidence and some evidence);** one category for uncertain findings **(equivocal evidence);** one category for no observable effects **(no evidence);** and one category for experiments that cannot be evaluated because of major flaws **(inadequate study).** These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as “were also related” to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as “may have been” related to chemical exposure.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on triethanolamine on May 22, 2003, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On May 22, 2003, the draft Technical Report on the toxicology and carcinogenesis studies of triethanolamine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

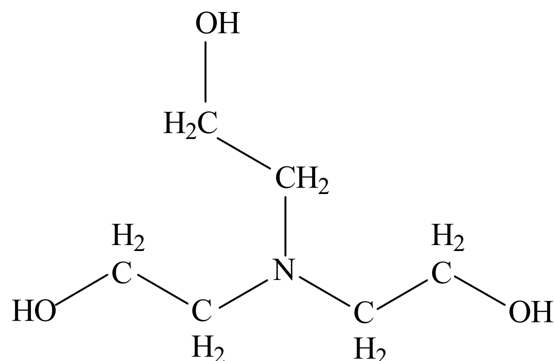
Dr. A. Suarez, NIEHS, introduced the toxicology and carcinogenesis studies of triethanolamine by describing the uses of the chemical. Dr. Suarez discussed the results of the previously published NTP Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (TR 449) in Rats and Mice. The previous mouse studies were considered inadequate due to infection of the mice with *Helicobacter hepaticus* and an associated hepatitis in male mice that confounded interpretation of a possible liver neoplasm response. Therefore, the current mouse studies were repeated using the same protocol. The proposed conclusions were *equivocal evidence of carcinogenic activity* of triethanolamine in male B6C3F_1 mice and *some evidence of carcinogenic activity* in female B6C3F_1 mice. Exposure to triethanolamine by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related nonneoplastic lesions at the site of application.

Drs. Walker, Roberts, and Carpenter, the three principal reviewers, all concurred with the proposed conclusions. Dr. Carpenter asked for an expansion in the discussion on the relative certainty regarding the hemangiosarcomas. Dr. J.R. Hailey, NIEHS, agreed to add more detail (see pages 33 and 36).

Dr. W.T. Allaben, NCTR, inquired about the extent of ulceration of the skin at the site of application. Dr. Hailey explained that even the most severe were characterized as occasional pinpoint focal crusts, with most of the skin relatively unaffected.

Dr. Walker moved, and Dr. Carpenter seconded, that the conclusions be accepted as written. The motion was accepted unamimously with eight votes.

INTRODUCTION



TRIETHANOLAMINE

CAS No. 102-71-6

Chemical Formula: $C_6H_{15}NO_3$ Molecular Weight: 149.19

Synonyms: Nitrilo-2,2′,2′′-triethanol; 2,2′,2′′-nitrilotriethanol; 2,2′,2′′-nitrilotrisethanol; TEA; triaethanolamin-NG; triethanolamin; triethylolamine; tri(hydroxyethyl)amine; 2,2′,2′′-trihydroxytriethylamine; trihydroxytriethylamine; tris(hydroxyethyl)amine; tris(2-hydroxyethyl)amine; trolamine
Trade names: Daltogen, Sterolamide, Thiofaco T-35

Chemical and Physical Properties

Triethanolamine is a colorless to pale yellow, viscous, hygroscopic liquid with a slight ammonia-like odor. It has a melting point of 21.6° C, boiling point of 335.4° C at 760 mm, a specific gravity of 1.124 (20/4° C), and vapor pressure less than 0.01 mm at 20° C. Triethanolamine is miscible in water, methanol, or acetone; slightly soluble in ether or benzene; and turns brown when exposed to air and light (*Merck Index*, 1996). It is combustible when heated, and it may decompose to oxides of nitrogen (Lewis, 1997).

Production, Use, and Human Exposure

Ethanolamines are produced on an industrial scale by aminating ethylene oxide with excess ammonia. Triethanolamine is separated from the mixture of amines generated by this reaction (mono- and diethanolamine) by distillation; in the United States, production of triethanolamine grew steadily from 13,000 tons in 1960 to 98,000 tons in 1990 (*Kirk-Othmer*, 1992). Worldwide production of triethanolamine is estimated to be 500,000 tons per year (United Nations Environment Program, cited by IARC, 2000).

Triethanolamine is used in manufacturing a variety of household products and in several industrial processes. It is a chemical intermediate for anionic and nonionic surfactants. Triethanolamine is also widely used in manufacturing emulsifiers and dispersing agents for household detergents and polishes, textiles (lubricants, dyes, and antistatic agents), agricultural herbicides, mineral and vegetable oils, paraffin and waxes, pharmaceutical ointments, and petroleum demulsifiers. Additional industrial uses of triethanolamine include as a vulcanization accelerator in the rubber industry; as a humectant and softening agent in hide tanning; and in manufacturing synthetic resins, plasticizers, adhesives, and sealants. It is a solvent for casein, shellac, and dyes. It also increases the penetration of organic liquids into wood

and paper. The metal chelating properties of triethanolamine are used in industrial applications such as corrosion inhibition, electroplating, metal cleaning and rust removal, and the preparation of photographic chemicals and soldering fluxes. The fatty acid salts of triethanolamine are used in lubricating and metalworking fluids (cutting oils). Addition of small amounts of triethanolamine or its salts reduces particle agglomeration during the grinding of cement and reduces set time and increases the early strength of concrete (*Kirk-Othmer,* 1978; *Hawley's*, 1987; *Merck Index*, 1996; Melnick and Tomaszewski, 1990). Articles intended for use in the production, processing, and packaging of food may contain triethanolamine (21 CFR, Parts 175, 176, 177, and 178).

Direct contact of the skin or eyes with undiluted triethanolamine represents the most significant risk for acute exposure in industrial settings. Substantial exposure to triethanolamine via inhalation appears unlikely due to its low vapor pressure (*Patty's*, 1981). From 1981 to 1983, The National Occupational Exposure Survey estimated that more than 1.7 million workers were potentially exposed to triethanolamine in the United States (NIOSH, 1990). The threshold limit value for triethanolamine is 5 mg/m^3 based primarily on skin and eye irritation (ACGIH, 2002).

Chronic exposure to triethanolamine may result from skin contact with household detergents, pharmaceutical ointments, cutting fluids, adhesives and sealants. However, dermal exposure to triethanolamine-containing consumer products (principally personal care products) is considered to be the primary route of general population exposure. Triethanolamine, in combination with fatty acids, is used extensively in cosmetic formulations including emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. The Cosmetic Ingredient Review (CIR) Expert Panel (1983) reported that, in 1981, triethanolamine was present in 2,757 cosmetic products at concentrations up to 5%; these products included creams, lotions, skin cleansers, shampoos, hair care and coloring agents, permanent wave lotions, deodorants, fragrances, makeup, nail polish and polish remover, and cuticle softeners and removers.

The CIR Expert Panel (1983) concluded that the use of mono-, di-, and triethanolamine is safe in cosmetic formulations designed for brief, discontinuous use followed by thorough rinsing of the skin. The CIR Expert Panel further concluded that the concentration of ethanolamine should not exceed 5% in cosmetic products intended for prolonged contact with the skin. In the presence of nitrite, oxides of nitrogen, or 2-bromo-2-nitropropane-1,3-diol, an antimicrobial agent used in cosmetics, di- and triethanolamine may be readily nitrosated to *N*-nitrosodiethanolamine, which is a known liver, kidney, and nasal carcinogen in laboratory animals (Hoffmann *et al.*, 1982; Preussmann *et al.*, 1982; Lijinsky and Kovatch, 1985). *N*-Nitrosodiethanolamine has been identified in a variety of cosmetic products at concentrations up to 48,000 ppb (Fan *et al.*, 1977); the CIR Expert Panel (1983) concluded, therefore, that di- and triethanolamines should not be used in cosmetic products that contain *N*-nitrosating agents as intentional ingredients or potential contaminants.

Environmental Impact

The environmental fate and aquatic toxicology of the alkanolamines have been reviewed (Davis and Carpenter, 1997). Triethanolamine may be released into the environment in emissions or effluents from manufacturing or industrial sites, from the disposal of consumer products containing triethanolamine, from the application of agricultural chemicals in which triethanolamine is used as a dispersing agent, or during use of an aquatic herbicide containing a copper-triethanolamine complex (*Hawley's*, 1987). Residual triethanolamine in soil may also leach into the groundwater. The half-life of triethanolamine in soil and water ranges from days to weeks; it biodegrades fairly rapidly following acclimation (HSDB, 2002). Ethanolamines have been shown to be selectively toxic to green algae (*Scenedesmus quadricauda*) (Bringmann and Kühn, 1980). In the atmosphere, triethanolamine primarily exists in the vapor phase; the vapor, which has a half-life of 4 hours, is expected to react with photochemically generated hydroxyl radicals in the atmosphere. The complete solubility of triethanolamine in water suggests that this compound may also be removed from the atmosphere by precipitation. Volatilization of triethanolamine from water and moist soil surfaces has been estimated to be negligible (Eisenreich *et al.*, 1981; Atkinson, 1987; HSDB, 2002).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

Triethanolamine is absorbed through the skin and in the gastrointestinal tract. In oral studies, 63% of

triethanolamine administered to Wistar rats was absorbed from the gastrointestinal tract within one hour after administration (IARC, 2000). In the skin, differences in the rate of absorption between F344 rats and C3H/HeJ mice have been described. In mice, most of the topically applied [^{14}C]-triethanolamine is absorbed, and only 6% to 11% is detected at the site of application after 48 hours (Stott *et al.,* 2000). In rats, absorption occurs more slowly and is less extensive (Melnick and Tomaszewski, 1990; IARC, 2000). Stott *et al.* (2000) reported similar levels of dermal absorption between C3H/HeJ mice and F344 rats 24 to 48 hours after dosing. In contrast, an absorption, distribution, metabolism, and excretion study by the National Toxicology Program (Appendix G) found that after 72 hours of exposure, only 20% to 30% of the applied dose of triethanolamine (68 or 276 mg/kg) was absorbed in rats and 80% was absorbed in mice (79 or 1,120 mg/kg).

These differences in absorption have been attributed either to the different doses used in comparative studies or to species-specific factors. In fact, an analysis of absorption data in Appendix G reveals that a 14-fold increase in concentration gives a 23-fold increase in absorption in mice; whereas in rats, a fourfold increase gives a sixfold increase in absorption. No differences in tissue distribution were noted after oral or dermal exposure (Appendix G).

The elimination of [^{14}C]-triethanolamine-derived radioactivity from the blood of mice after a 1 mg/kg intravenous injection displays two-phase elimination kinetics with an initial rapid distribution phase (0.3-hour half-life) followed by a slower elimination phase (10-hour half-life). Kinetics following an unoccluded dermal application of neat triethanolamine (200 mL/kg) was described as an initial rapid absorption phase (0.7-hour half-life) and two elimination phases with half-lives of 1.9 and 31 hours (Stott *et al.,* 2000). The dermal absorption study was unoccluded, so it may be expected that some triethanolamine was orally absorbed through grooming.

Excretion of [^{14}C]-triethanolamine is similar among rats and mice. Following a dermal dose of 1,000 mg/kg, mice excreted approximately 60% of the radioactivity in the urine and 20% in the feces 48 hours after dosing; rats excreted 54% and 9% in the urine and feces, respectively (Stott *et al.,* 2000). Kohri *et al.* (1982) reported that urinary excretion of [^{14}C]-triethanolamine in rats occurred primarily as the parent compound with a small amount of glucoronide metabolite.

Humans

No information on the absorption, distribution, metabolism, or excretion of triethanolamine in humans was found in the literature.

TOXICITY

Experimental Animals

The toxicity of triethanolamine was the subject of a review by Knaak *et al.* (1997). The acute and chronic toxicity of triethanolamine is generally considered to be low (Kindsvatter, 1940; Melnick and Tomaszewski, 1990). Triethanolamine toxicity has been demonstrated in animals following administration by injection and oral routes (gavage, feed, and drinking water) and by dermal application. In a study comparing the relative toxicities of the ethanolamines (*Patty's*, 2000), symptoms in dogs following intravenous injection included increased blood pressure, diuresis, salivation, and pupillary dilation; larger doses caused sedation, coma, and death following a decrease in blood pressure and cardiac collapse. Symptoms were most severe with monoethanolamine and less severe with diethanolamine and equivalent doses of triethanolamine.

The acute oral LD_{50} of triethanolamine was reported to be 8 to 9 g/kg in albino rats and 8 g/kg in guinea pigs (Kindsvatter, 1940; Smyth *et al.*, 1951). Gross lesions in the animals that died were confined to the gastrointestinal tract and included gastric dilatation, congestion, and focal hemorrhage in the stomach and dilatation of intestinal blood vessels. Kindsvatter (1940) suggested that the acute toxicity of triethanolamine was related to its alkalinity, based on the survival of one guinea pig fed 10 g/kg neutralized with hydrochloric acid; this dose exceeds the oral LD_{50} (8 g/kg) of triethanolamine when administered as the free base. The acute oral LD_{50} values for triethanolamine ranged from 4.2 to 11.3 g/kg in rats and 5.4 to 7.8 g/kg in mice (BIBRA, 1990).

In a 90-day study in Carworth-Wistar rats administered triethanolamine in feed at daily doses of 5 to 2,610 mg/kg, the no-observed-effect level (NOEL) was 80 mg/kg. Decreased body weight gains were observed in rats administered 1,270 mg/kg or above. Microscopic lesions of the kidney, liver, lung, or small intestine and a low incidence of mortality occurred at a concentration of 730 mg/kg or above. Liver and kidney weight effects occurred at concentrations as low as 170 mg/kg (Smyth *et al.*, 1951). In other studies (Kindsvatter, 1940), doses ranging from 200 to 1,600 mg/kg were administered to

albino rats daily in feed for up to 17 weeks or to guinea pigs 5 days per week by gavage for up to 120 doses. Slight, reversible changes were present in the kidney (cloudy swelling of the convoluted tubules and Henle's loop) at all doses and in the liver (hepatocellular cloudy swelling and fatty change) at doses of 400 mg/kg and higher. Although liver toxicity was not apparent in a 2-year study with Fischer 344/DuCrj rats administered 1% or 2% triethanolamine in drinking water *ad libitum*, the occurrence of dose-related kidney toxicity (acceleration of chronic nephropathy, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis with or without papillary necrosis) indicated that even the 1% dose level was not well tolerated by rats (Maekawa *et al.*, 1986); effects were more severe in females than in males. Due to increased mortality and decreased body weight gains in females that received 2% triethanolamine, doses administered to females were halved from week 69 to the end of the study. In contrast, $B6C3F_1$ mice tolerated the same concentrations of triethanolamine in drinking water for 82 weeks without adverse effects on survival or organ weights and with no increased incidences of histopathologic lesions (Konishi *et al.*, 1992); however, body weights of mice that received 2% were slightly less than those of the controls.

The dermal toxicity of triethanolamine has been evaluated in mice, rats, rabbits, and guinea pigs under various experimental conditions. Guinea pigs dosed with 8 g/kg of undiluted triethanolamine daily by dermal application, 5 days per week, died after 2 to 17 applications (Kindsvatter, 1940). Histopathologic changes included generalized congestion of the lungs, kidneys, liver, adrenal glands, and peritoneum; extravasation of fibrin into the alveoli of the lungs; cloudy swelling of the kidneys and liver; fatty change in the liver; and cellular infiltration and inflammation at the site of application, indicating that dermal absorption of triethanolamine is capable of producing systemic toxicity (Kindsvatter, 1940; Melnick and Tomaszewski, 1990).

The acute dermal toxicity of a single 2 g/kg application of undiluted triethanolamine was evaluated over a 24-hour period with a closed-patch test in rabbits (CIR, 1983). Triethanolamine was applied to six rabbits with intact skin and six with abraded skin. Mild to moderate erythema without edema occurred on both intact and abraded skin and resolved within 10 days. In another dermal study, a single application of 560 mg/kg to rabbits resulted in erythema and slight edema at the application site. Dermal applications of 2 mL/kg per day of a 2.5% aqueous solution of triethanolamine for 28 days produced only mild dermatitis in New Zealand rabbits (CIR, 1983). Triethanolamine (1% to 100%), applied dermally to male C3H mice 5 days per week for 2 weeks in 50 µL acetone, caused mild epidermal hyperplasia at the site of application with dosage solutions as low as 25% (cited by Melnick and Tomaszewski, 1990). In a follow-up study in which male and female C3H mice received dermal applications of 0%, 10%, 33%, or 100% triethanolamine in 50 µL acetone three times per week for 13 weeks, mild hyperplasia at the application site was observed in all dosed groups (Melnick and Tomaszewski, 1990; DePass *et al.*, 1995).

In a combined dermal and drinking water study, CBA × C57Bl6 mice received dermal applications of a 6.5% or 13% aqueous solution of triethanolamine, 1 hour per day, 5 days per week for 6 months, with or without additional oral administration of 1.4 mg/L in the drinking water (Kostrodymova *et al.*, 1976; CIR, 1983). No toxic effects were present in mice that received the 6.5% solution. However, functional changes in the liver and central nervous system occurred 1 month after treatment began with the 13% solution, with or without additional triethanolamine in the drinking water, indicating that systemic toxicity had resulted from percutaneous absorption. Clinical pathology changes at 3 months included elevated lymphocyte and segmented neutrophil counts.

The eye irritation potential of triethanolamine or cosmetics containing the chemical has been evaluated in rabbits and rhesus monkeys; these studies have been reviewed by the CIR Expert Panel (1983). In a study with albino rabbits, moderate irritation occurred when 0.1 mL triethanolamine was instilled (Griffith *et al.*, 1980); application of 0.01 mL caused only negligible damage. Application of 0.02 mL undiluted triethanolamine to the cornea of the rabbit eye with the lids retracted caused necrosis of 63% to 87% of the cornea; this reaction was graded as 5 on a scale of 1 to 10 (Carpenter and Smyth, 1946). Application of a 0.023 M aqueous solution of triethanolamine to rabbit eyes, following removal of the corneal epithelium to facilitate penetration, caused essentially no injuries when the solution was adjusted to pH 10; application of the same solution adjusted to pH 11 caused moderate corneal swelling and hyperemia of the iris and conjunctiva that reversed within 1 week (Grant, 1974).

Skin and eye irritation in rabbits were evaluated in a study comparing the effects of ethanolamines (mono-, di-, and triethanolamine) and three mixtures containing 69%, 74%, or 87% triethanolamine plus varying proportions of other ethanolamines (Dutertre-Catella *et al.*, 1982). Eye irritation was rated maximum for monoethanolamine, severe for diethanolamine, mild for the 69% and 74% mixtures, and minimum for triethanolamine and the 87% mixture. Skin irritation was rated severe for monoethanolamine, moderate for diethanolamine and the 69% mixture, and slight for triethanolamine and the 74% and 87% mixtures. Although skin sensitization occurs in humans, no skin sensitizing responses or delayed hypersensitivity reactions occurred in studies of guinea pigs treated dermally with 5% to 100% triethanolamine (one application per week for 3 weeks; up to 6 hours per application) and subsequently challenged with 25% to 100% triethanolamine after 1 to 3 weeks (CIR, 1983).

No clinical evidence of systemic toxicity or histopathologic lesions was observed when hair dye preparations containing 0.1% to 1.5% triethanolamine were applied to the clipped backs and sides of New Zealand white rabbits at doses of 1 mg/kg twice weekly for 13 weeks, with or without prior abrasion of the skin (Burnett *et al.*, 1976). However, in a similar 13-week rabbit study in which cosmetic formulations containing 14% triethanolamine stearate were applied to the clipped back five times per week in doses of 1 or 3 mg/kg, mild to moderate skin irritation occurred; the irritation, which cleared within 72 hours, was followed by moderate to heavy scaling (CIR, 1983). Signs of systemic toxicity included lower body weight and significantly greater kidney weights at the 3 mg/kg dose.

NTP (1999) examined both the local and systemic toxicity of triethanolamine in prechronic studies. Fischer 344/N rats received dermal applications of triethanolamine either undiluted (2,000 mg/kg) or in acetone (125 to 1,000 mg/kg) once per day, 5 days per week. Rats receiving 2,000 mg/kg gained less weight than controls and had hypertrophy of the pituitary gland. Additional lesions seen in rats receiving 2,000 mg/kg and lower doses included increased kidney weights and acanthosis and chronic inflammation at the skin site of application. B6C3F$_1$ mice were treated topically with 4,000 mg/kg (neat) or 250 to 2,000 mg/kg (diluted) triethanolamine. Weight gains were marginally less at the top concentration, and these animals also exhibited increased liver and kidney weights and chronic active inflammatiion at the skin site of application. Skin lesions in mice receiving lower doses of triethanolamine were generally limited to minimal acanthosis.

In subsequent studies, doses of 32 to 125 mg/kg in male rats and 63 to 250 mg/kg in female rats were used to investigate the effects of triethanolamine applied topically after 103 weeks of treatment (NTP, 1999). Inflammation (males and females) and ulceration (females) at the site of application were common findings at the 15-month interim evaluation, and a spectrum of lesions at the site of application was observed at the end of the 2-year study. These included acanthosis, chronic active inflammation, erosions, and ulcers. These occurred primarily in females and in 125 mg/kg males. B6C3F$_1$ mice were also treated chronically with triethanolamine at doses of 200 to 2,000 mg/kg in males and 100 to 1,000 mg/kg in females. Skin lesions at the site of application included acanthosis and chronic inflammation. These were generally minimal to mild at 15 months and 2 years and again showed that mice were less sensitive to triethanolamine than were rats.

More recently, triethanolamine was evaluated in a genetically modified mouse skin papilloma model (Spalding *et al.*, 2000). Doses up to 30 mg of triethanolamine were administered topically to groups of 15 to 20 female Tg.AC mice five times per week for 20 weeks. The experimental design also included positive and negative controls. In contrast to the positive controls, which developed multiple papillomas, there were no increases in the incidences of skin tumors in mice receiving triethanolamine.

Humans

There is no appreciable hazard to workers from normal industrial use of ethanolamines (*Kirk-Othmer*, 1999). However, these compounds may cause serious toxic effects when ingested, as well as local injury to the mouth, throat, and digestive tract. At ordinary temperatures, triethanolamine presents no hazard from vapor inhalation, but excessive vapor concentrations may occur when triethanolamine is heated. These vapors are irritating to the eyes and nose. Triethanolamine is a skin and eye irritant; however, it is less irritating to the skin and mucous membranes than most amines.

In a series of patch tests on healthy volunteers, the highest nonirritant concentration of triethanolamine, applied in petrolatum for 48 hours, was determined to be 50%

(Meneghini *et al.*, 1971). In a different test, the irritancy potential of triethanolamine was designated as slight (5% concentration) or marked (10% concentration) when applied topically in ethanol within a chamber to the scarified forearm skin of volunteers once daily for 3 days; the threshold concentration for skin irritation was 100% on intact skin and 5% (in ethanol) on scarified skin (Frosch and Kligman, 1976).

There have been no reports of industrial injuries from triethanolamine (*Patty's*, 2000). However, Shrank (1985) reported that a lathe operator became sensitized to triethanolamine, which was an ingredient in a cutting oil, and 47 positive reactions to triethanolamine (10% in an aqueous solution) occurred in patch tests of 230 metal workers with occupational dermatitis (Alomar *et al.*, 1985). In this study, 43% of all positive responses were to triethanolamine. Triethanolamine was also the most frequent sensitizer in a study in which patients with suspected cosmetic- or medicine-related contact dermatoses were patch tested with common emulsifying agents (Tosti *et al.*, 1990). It has been identified as a causative agent in patients with eczema or allergic contact dermatitis (Venediktova and Gudina, 1976; Angelini *et al.*, 1985; Jones and Kennedy, 1988) and in a curious case of intractable sneezing caused by exposure to a laundry detergent (Herman, 1983).

In a study designed to evaluate allergic contact dermatitis to substances commonly found in pharmaceutical ointments, a 24-hour patch test with a 1% aqueous solution of triethanolamine in 773 patients gave positive reactions in four (0.5%) of these patients (Iden and Schroeter, 1977). Positive reactions also occurred in 2% of 100 subjects in another study with a 48-hour patch test using 5% triethanolamine in petrolatum (Fisher *et al.*, 1971; Iden and Schroeter, 1977). In clinical tests with triethanolamine and cosmetic products containing triethanolamine, mild skin irritation occurred at concentrations above 5%, but there was little skin sensitization. In addition, there was no evidence of phototoxicity or photosensitization reactions with products that contained up to 20% triethanolamine (CIR, 1983). However, based on positive skin sensitivity reactions (patch-test results) in 1.6% of a patient population with eczematous dermatitis who were tested with 5% triethanolamine in petrolatum, Meneghini *et al.* (1971) recommended restricting the use of triethanolamine in cosmetics and pharmaceutical preparations.

Triethanolamine has been given a toxic hazard rating of slightly toxic, with a probable oral lethal dose in humans of 5 to 15 g/kg, which corresponds to between 1 pint and 1 quart for a 70 kg (150 lb) person (Gosselin *et al.*, 1984). Dreisbach (1980) estimated the lethal dose in humans to be 50 g. Assuming complete dermal absorption, a human weighing 50 kg would receive an approximate dose of 10 mg/kg through the use of 10 g of cosmetics containing 5% triethanolamine.

Reproductive and Developmental Toxicity

Experimental Animals

Triethanolamine has been shown to stimulate neuritogenesis in cultured chick embryo ganglia (Sisken *et al.*, 1985). However, it was embryotoxic when injected into 3-day chick embryos; the LD_{50} value (the dose causing early death in 50% of the embryos) was 3 µmol (447 µg) per egg. Eleven days after the triethanolamine injection, there was no significant increase in the incidence of chick embryo malformations (Korhonen *et al.*, 1983; cited by Melnick and Tomaszewski, 1990).

In an *in vivo* assay for potential adverse reproductive effects in mice, di- and triethanolamine, administered daily by gavage on gestation days 6 through 15 in doses of 1,125 mg/kg per day, had no effect on maternal mortality, the number of viable litters, litter size, or survival and body weight of the pups. However, similar administration of 850 mg/kg per day of monoethanolamine resulted in 16% mortality in dams and fewer viable litters (NIOSH, 1987). A preliminary developmental toxicity test in mice, used in conjunction with a scoring system of indices of developmental toxicity, resulted in a classification of low priority for further study of monoethanolamine, intermediate priority or "no decision" for triethanolamine, and high priority for diethanolamine (York *et al.*, 1988).

In mating trial studies in male and female Fisher 344 rats, 0.5 g/kg of triethanolamine in acetone, applied dermally to the interscapular area of the clipped back in an approximate volume of 1.8 mL/kg daily for 10 weeks prior to mating, during breeding, and through gestation and lactation for females, had no effect on mating, fertility, or offspring growth and survival. In similar studies with Swiss (CD-1®) mice administered daily

applications of 2 g/kg in an approximate volume of 3.6 mL/kg, no chemical-related effects occurred other than ruffled fur in females and irritation at the application site in males and females (Battelle, 1988a,b).

No embryotoxic or teratogenic effects were produced by topical administration of semipermanent hair dye preparations (2 mL/kg) containing 0.1% to 1.5% triethanolamine to the shaved backs of pregnant Charles River CD rats on gestation days 1, 4, 7, 10, 13, 16, and 19 (Burnett *et al.*, 1976).

Humans

No information related to the reproductive or developmental toxicity of triethanolamine in humans was found in the literature.

CARCINOGENECITY

Experimental Animals

Triethanolamine was not carcinogenic in Fischer F344/DuCrj rats when administered *ad libitum* in drinking water at dose levels of 1% or 2%, but was nephrotoxic, especially in females (Maekawa *et al.*, 1986). Due to increased mortality associated with nephrotoxicity in females and decreased body weight gain in females in the 2% group, the doses of triethanolamine administered to the female groups were reduced by half after week 68 of the study. There were no statistically significant increased incidences of primary neoplasms in exposed groups compared to the controls when analyzed by the chi-square test. Because of nephrotoxicity, which appeared to have an adverse effect on the life expectancy of exposed animals, an age-adjusted statistical analysis was performed. The results showed a positive trend ($P<0.05$) in the incidence of hepatic neoplasms in males and uterine endometrial sarcomas and renal tubule adenomas in females. However, the incidences of these neoplasms in the control groups were lower than those in historical controls. In a similar study, triethanolamine had no carcinogenic activity in $B6C3F_1$ mice when administered in drinking water at concentrations of 1% or 2% for 82 weeks (Konishi *et al.*, 1992). Triethanolamine was not carcinogenic in male CBA × C57Bl6 mice when applied dermally for 14 to 18 months (Kostrodymova *et al.*, 1976; CIR, 1983).

Incidences of malignant lymphoma, particularly thymic lymphoma, were increased in female, but not in male, ICR-JCL mice fed diets containing 0.03% or 0.3% triethanolamine throughout their life spans (Hoshino and Tanooka, 1978). The incidences of total malignant neoplasms in treated female mice were significantly greater than the control incidence ($P<0.01$); the incidences were 1/36 in controls, 10/37 in the 0.03% group, and 13/36 in the 0.3% group. In another long-term study with ICR mice (Inai *et al.*, 1979), the combined incidence of thymic lymphoma and nonthymic leukemia in control females at 109 weeks was 5/15. This rate is 10 times greater than the rate observed in the female control group of the Hoshino and Tanooka study, and is similar to that reported for triethanolamine-treated females.

Rust-proofing cutting fluid (containing low levels of triethanolamine, sodium nitrite, and polyethylene glycol) was carcinogenic in male Wistar rats (Wang *et al.*, 1988). Groups of 40 rats were administered either undiluted cutting fluid or a threefold dilution of the fluid in water *ad libitum* for 2 years. Treated rats had increased incidences of neoplasms, particularly pancreatic carcinoma. The total incidences of malignant neoplasms were 0% in the control group, 10% in the group given diluted cutting fluid, and 27.5% in the group that received the undiluted fluid. In another group of rats exposed to undiluted cutting fluid supplemented with ascorbic acid, the total incidence of malignant neoplasms was 1/40 (2.5%). Based on the protective action of ascorbic acid in this study, Wang *et al.* (1988) concluded that the carcinogenic agent was a nitrosamine formed *in vivo*; the inhibitory action of ascorbic acid on the *in vivo* formation of nitroso compounds has been documented (Mirvish *et al.*, 1975). Because the cutting fluid contained triethanolamine and sodium nitrite, the most probable nitrosamine formed during this study was *N*-nitrosodiethanolamine. However, the neoplasms induced in rats in previous experiments with *N*-nitrosodiethanolamine were primarily hepatocellular carcinomas, not pancreatic carcinomas (Lijinsky and Kovatch, 1985).

No neoplastic effects occurred in female Fischer 344/N rats that received dermal applications of 63, 125, or 250 mg triethanolamine/kg body weight for 2 years (NTP, 1999); body weights of the highest dose group were 7% lower than those of the vehicle controls at the end of the study. Male rats treated with 32, 63, or 125 mg/kg had marginal increases in the incidences of renal tubule adenoma. Male $B6C3F_1$ mice received 200, 630, or 2,000 mg/kg triethanolamine by dermal application and female mice received 100, 300, or 1,000 mg/kg;

skin inflammation and liver neoplasms occurred in males and females. However, the 2-year study in mice was considered inadequate due to infection with *Helicobacter hepaticus.*

Humans

In an epidemiology study conducted by Järvholm *et al.* (1986), the mortality and cancer morbidity in 219 men exposed to cutting fluids for at least 5 years, including at least 1 year of exposure to a cutting fluid containing both amines and nitrites (primarily ethanolamines and sodium nitrite), were not significantly different from those of the general population. Although the results indicate that the use of cutting fluids in this industry does not lead to an increased risk of cancer, the authors were unable to exclude the possibility of an increased risk for cancer of a specific site because of the small sample population. Although an association between exposure to metal-working fluids and cancer has been reported (Kazerouni *et al.,* 2000), no conclusions can be drawn regarding the specific exposure to triethanolamine.

Genetic Toxicity

The limited information on the mutagenicity of triethanolamine indicates that the chemical is not genotoxic. A review of the toxicity of triethanolamine, including genetic toxicity, was published by IARC (2000). Triethanolamine did not induce DNA damage in *Escherichia coli* (Inoue *et al.*, 1982), mutations in *Salmonella typhimurium* (Inoue *et al.*, 1982; Dean *et al.*, 1985; Mortelmans *et al.*, 1986), or gene conversion in *Saccharomyces cerevisiae* (Dean *et al.*, 1985). No induction of sister chromatid exchanges occurred in cultured Chinese hamster ovary cells treated with triethanolamine (Galloway *et al.*, 1987), and results of tests for induction of chromosomal aberrations in cultured rat liver cells (Dean *et al.*, 1985) and cultured Chinese hamster cells (Inoue *et al.*, 1982; Galloway *et al.*, 1987) were also negative. The *S. typhimurium* tests and the rodent cell cytogenetic tests were conducted with and without S9 metabolic activation enzymes. No increase in the frequency of sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* administered triethanolamine by feeding or injection (Yoon *et al.*, 1985).

Study Rationale

The National Cancer Institute nominated triethanolamine for study because of its widespread use in cosmetics and other consumer products, its high potential for worker exposure due to its many industrial uses, and its potential for conversion to the carcinogen *N*-nitrosodiethanolamine. Concern was also prompted by the increased incidences of lymphoma and total malignant neoplasms in female ICR-JCL mice that received 0.03% or 0.3% triethanolamine in the diet (Hoshino and Tanooka, 1978). Based on these considerations, the NTP conducted dermal studies in order to evaluate the toxicity and potential carcinogenic activity of triethanolamine in mice and rats. Dermal application was chosen as the route of exposure to mimic the primary human exposure to triethanolamine and because considerable systemic exposure is achieved with this route.

NTP (1999) reported equivocal evidence of carcinogenic activity of triethanolamine in male F344/N rats. However, the study in B6C3F$_1$ mice was considered inadequate due to the presence of *H. hepaticus* infection, which complicated interpretation of the relationship between triethanolamine administration and liver neoplasms. Evaluating the role of triethanolamine in the development of liver neoplasms in uninfected mice is necessary to complete the characterization of the carcinogenic hazard of triethanolamine.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Triethanolamine

Triethanolamine was obtained from Texaco Chemical Company (Division of Texaco, Inc., Bellaire, TX) in one lot (7G-60). Identity, purity, and moisture content analyses were conducted by the analytical chemistry laboratory (Research Triangle Institute, Research Triangle Park, NC); identity, purity, and stability analyses were conducted by the study laboratory (Appendix D). Special analyses of diethanolamine and nitrosamine impurities in the bulk chemical were conducted by the analytical chemistry laboratory and Covance Laboratories, Inc. (Madison, WI). Reports on analyses performed in support of the triethanolamine study are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as triethanolamine using ultraviolet/visible, infrared, and proton nuclear magnetic resonance spectroscopy and high- and low-resolution mass spectrometry. Karl Fischer titration indicated 0.18% water. The purity of lot 7G-60 was determined using gas chromatography and high-performance liquid chromotography (HPLC).

Gas chromatography indicated one major peak and no impurities by two systems and one major peak and one impurity with an area of 0.88% relative to the major peak area by a third system; the impurity was determined to be diethanolamine. Gas chromatography indicated that the compound contained no impurity other than diethanolamine at a concentration greater than 0.1% by a fourth system. HPLC indicated no measurable impurities with chromophores. The overall purity of lot 7G-60 was determined to be greater than 99%.

A special HPLC/mass spectrometric study was conducted to determine the relative concentration of diethanolamine as an impurity in the test chemical and to conduct an accelerated stability study. Analysis showed that diethanolamine constituted 0.491% (weight percent relative to the test chemical weight) of the test chemical. Solutions of triethanolamine were prepared in acetone or 95% ethanol and stored in sealed glass containers at 32° to 36° C, protected from light, for 1.6 hours or 11 days. After 11 days of storage, both solutions showed slight increases in diethanolamine concentrations compared to those measured at time 0; no differences were noted following 1.6 hours of storage.

The concentrations of nonpolar nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitrosodi-n-propylamine, *N*-nitrosodi-n-butylamine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, and *N*-nitrosomorpholine) and the polar nitrosamine *N*-nitrosodiethanolamine were determined in lot 7G-60 by gas chromatography and HPLC. No nonpolar or polar nitrosamines were present at concentrations greater than the limits of detection (0.1 and 1.0 ppm, respectively).

Stability studies of the bulk chemical were performed on lot 03601CN (not used in the current study) using gas chromatography. These studies indicated that triethanolamine was stable as a bulk chemical for 14 days when stored in amber glass vials at 5°, 25°, and 60° C, when compared to a sample stored at –20° C. To ensure stability, triethanolamine was stored at room temperature in amber glass containers with Teflon®-lined lids. No degradation of triethanolamine was observed.

Acetone

Acetone was obtained in four lots (NE0173, NV0163, OG0513, and OX0312) from Spectrum Chemical Manufacturing Corporation (Gardena, CA). Identity and purity analyses of each lot were conducted by the study laboratory.

The chemical, a clear liquid, was identified as acetone using infrared spectroscopy. The purity of each lot was determined using gas chromatography. No significant impurities were detected in any lot. The overall purity of each lot was determined to be greater than 99%.

To ensure stability, the bulk chemical was stored at room temperature in amber glass bottles. No degradation of the acetone was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared approximately every 2 weeks by mixing triethanolamine and acetone to give the required concentration (Table D3). The dose formulations were stored for up to 21 days at 5° C in amber glass bottles with Teflon®-lined lids.

Stability studies of 10 mg/mL dose formulations in acetone were performed by Midwest Research Institute (Kansas City, MO) using gas chromatograpy. The dose formulations were stored in amber glass bottles with Teflon®-lined lids under nitrogen headspace for up to 21 days at 5° C, and for at least 3 hours under animal room conditions (open to air and light).

Periodic analyses of the dose formulations of triethanolamine were conducted by the study laboratory with gas chromatography. During the 2-year study, the dose formulations were analyzed approximately every 8 or 12 weeks; animal room samples were also analyzed periodically (Table D4). Of the dose formulations analyzed, all 66 were within 10% of the target concentrations; 18 of 24 animal room samples were within 10% of the target concentrations. The other six dose formulations were higher than the target concentrations and, with one exception, occurred with the first set of dose formulations used in the study. The change in concentrations was due to evaporation of the acetone during administration and subsequently, steps were taken to minimize this effect. The maximum was 15% higher than the prepared concentration.

2-Year Study

Study Design

Groups of 50 male and 50 female mice received dermal applications of 0, 200, 630, or 2,000 mg/kg (males) and 0, 100, 300, or 1,000 mg/kg (females) triethanolamine in acetone, 5 days per week, for 104 (males) or 104 to 105 (females) weeks; the dosing volume was 2 mL/kg. Doses were applied to an area extending from the animal's mid-back to the intrascapular region; the site of application was clipped approximately once per week during the study.

Source and Specification of Animals

Male and female B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year study. Mice were quarantined for 14 (males) or 13 (females) days before the beginning of the study. Five male and five female mice were randomly selected for parasite evaluation and gross observation of disease. Mice were approximately 6 weeks old at the beginning of the study. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

Animal Maintenance

Mice were housed individually. Feed and water were available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix E.

Clinical Examinations and Pathology

All mice were observed twice daily and were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the study. Clinical findings were recorded on day 29, monthly thereafter, and at the end of the study.

Complete necropsies and microscopic examinations were performed on all mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for

accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the liver and skin.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

Table 1
Experimental Design and Materials and Methods in the 2-Year Dermal Study of Triethanolamine

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

Strain and Species
B6C3F_1 mice

Animal Source
Taconic Laboratory Animals and Services (Germantown, NY)

Time Held Before Studies
14 (males) or 13 (females) days

Average Age When Studies Began
6 weeks

Date of First Dose
September 24 (males) or 23 (females), 1998

Duration of Dosing
104 (males) or 104 to 105 (females) weeks

Date of Last Dose
September 17-19 (males) or 19-21 (females), 2000

Necropsy Dates
September 18-20 (males) or 20-22 (females), 2000

Average Age at Necropsy
110 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
Irradiated NTP-2000 pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly

Water
Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

Cages
Polycarbonate (Lab Products, Inc., Montville, NJ), changed weekly

Bedding
Irradiated Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed weekly

Table 1
Experimental Design and Materials and Methods in the 2-Year Dermal Study of Triethanolamine

Cage Filters
Spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks

Racks
Stainless steel (Lab Products, Inc., Montville, NJ), changed and rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
0, 200, 630, or 2,000 mg/kg (males) and 0, 100, 300, or 1,000 mg/kg (females) in acetone by dermal application (dosing volume 2 mL/kg)

Type and Frequency of Observation
Observed twice daily; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the study; clinical findings were recorded on day 29, monthly thereafter, and at the end of the study.

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsy was performed on all mice.

Histopathology
Complete histopathology was performed on all mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eye, gallbladder, harderian gland, heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung with bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin (site of application), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, and B5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3 and B3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3 and B3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm,

proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1– P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber than the NIH-07 diet used previously in toxicity and carcinogenicity studies (Rao, 1996, 1997). The current NTP historical database contains all 21 studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison. The triethanolamine study is the only dermal study in the database; therefore, overall incidences for all routes have been used in this Technical Report.

Quality Assurance Methods

The 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of triethanolamine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium,* sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster,* and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix C.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

2-YEAR STUDY

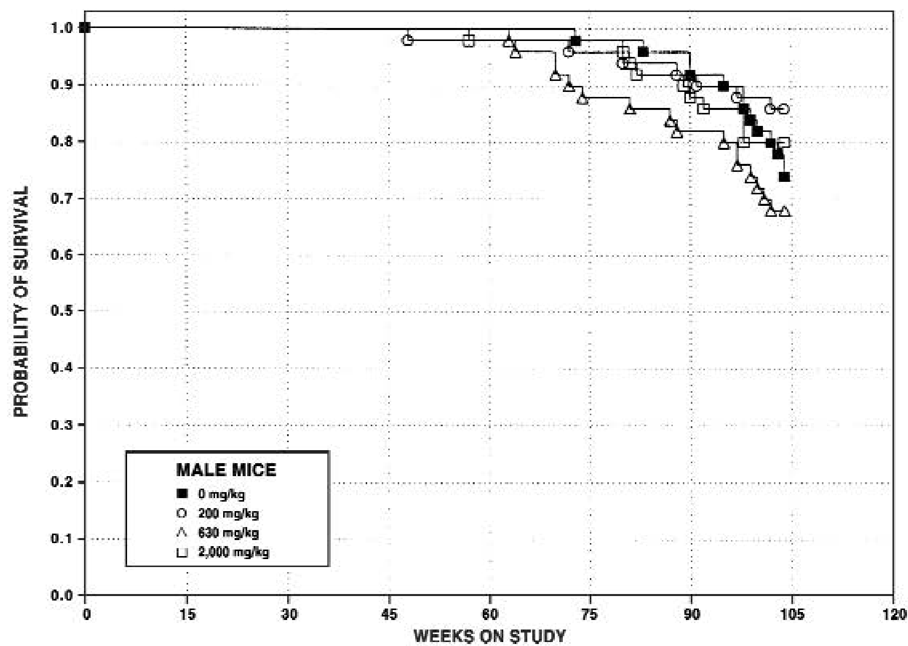
Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 1). Survival of all dosed groups was similar to that of the vehicle control groups.

TABLE 2
Survival of Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Male				
Animals initially in study	50	50	50	50
Moribund	5	2	6	8
Natural deaths	8	5	10	2
Animals surviving to study termination	37	43	34	40
Percent probability of survival at end of study[a]	74	86	68	80
Mean survival (days)[b]	710	705	683	701
Survival analysis[c]	P=1.000N	P=0.254N	P=0.492	P=0.743N
	Vehicle Control	**100 mg/kg**	**300 mg/kg**	**1,000 mg/kg**
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	0	0	0	1
Moribund	8	10	5	10
Natural deaths	7	6	4	7
Animals surviving to study termination	35[e]	34	41	32
Percent probability of survival at end of study	70	68	82	65
Mean survival (days)	692	682	686	687
Survival analysis	P=0.759	P=1.000	P=0.293N	P=0.865

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dosed group is indicated by **N**.
[d] Censored from survival analyses
[e] Includes one animal that died during the last week of the study



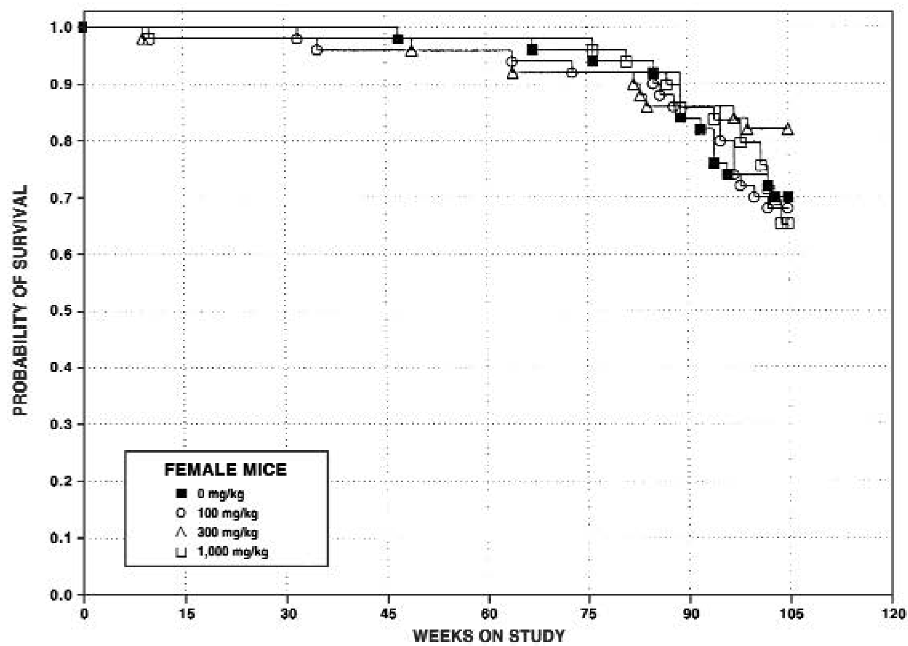


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Mice Administered Triethanolamine Dermally for 2 Years

Body Weights and Clinical Findings

Body weights of 2,000 mg/kg males were less than those of the vehicle controls from weeks 17 to 37 and at the end of the study, and body weights of dosed groups of females were similar to those of the vehicle controls throughout the study (Tables 3 and 4; Figure 2). Treatment-related clinical findings included irritation of the skin at the site of application in dosed males and 300 and 1,000 mg/kg females consisting of small, brown, crusty, scab-like patches. Skin irritation increased with increasing dose and was more severe in males than in females; these lesions were not considered sufficiently severe to require early termination of any of the mice in the study.

Table 3
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Triethanolamine

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	200 mg/kg Av. Wt. (g)	200 mg/kg Wt. (% of controls)	200 mg/kg No. of Survivors	630 mg/kg Av. Wt. (g)	630 mg/kg Wt. (% of controls)	630 mg/kg No. of Survivors	2,000 mg/kg Av. Wt. (g)	2,000 mg/kg Wt. (% of controls)	2,000 mg/kg No. of Survivors
1	22.8	50	22.9	100	50	22.9	100	50	22.8	100	50
2	23.8	50	23.8	100	50	23.7	100	50	24.0	101	50
3	24.9	50	25.2	101	50	25.1	101	50	25.2	101	50
4	26.3	50	26.6	101	50	26.5	101	50	26.6	101	50
5	27.5	50	27.7	101	50	27.6	100	50	27.8	101	50
6	28.5	50	28.0	98	50	28.7	101	50	28.3	99	50
7	29.3	50	29.4	100	50	29.4	100	50	28.9	99	50
8	30.3	50	29.9	99	50	30.4	100	50	29.8	98	50
9	31.4	50	30.8	98	50	31.2	99	50	30.4	97	50
10	32.6	50	31.8	98	50	32.4	99	50	31.3	96	50
11	33.7	50	32.6	97	50	33.2	99	50	32.1	95	50
12	34.8	50	33.6	97	50	34.1	98	50	32.8	94	50
13	35.1	50	34.1	97	50	34.4	98	50	33.3	95	50
17	39.4	50	38.1	97	50	38.6	98	50	36.2	92	50
21	42.5	50	40.6	96	50	41.6	98	50	38.1	90	50
25	45.2	50	43.8	97	50	43.5	96	50	40.9	91	50
29	47.5	50	46.5	98	50	46.9	99	50	43.3	91	50
33	49.0	50	48.0	98	50	48.6	99	50	45.4	93	50
37	50.2	50	49.6	99	50	49.9	99	50	47.3	94	50
41	50.1	50	49.7	99	50	50.9	102	50	48.8	97	50
45	51.4	50	50.4	98	50	51.6	100	50	50.2	98	50
49	51.5	50	50.8	99	49	52.1	101	50	51.0	99	50
53	50.6	50	50.0	99	49	51.3	101	50	50.8	100	50
57	51.0	50	50.5	99	49	51.4	101	50	50.2	98	50
61	51.6	50	51.1	99	49	52.0	101	50	50.7	98	49
65	51.3	50	51.6	101	49	52.4	102	48	51.1	100	49
69	52.0	50	52.6	101	49	52.2	100	48	50.8	98	49
73	52.3	50	53.1	102	48	54.3	104	45	51.7	99	49
77	53.4	49	54.0	101	48	54.2	102	44	52.3	98	49
81	52.8	49	53.1	101	47	53.8	102	44	51.6	98	48
85	51.8	48	52.9	102	47	53.8	104	43	51.7	100	46
89	51.9	48	52.7	102	46	53.0	102	41	50.2	97	46
93	51.9	46	53.4	103	45	53.1	102	41	50.1	97	43
97	50.4	45	51.0	101	45	50.4	100	39	47.1	94	43
101	51.0	41	50.9	100	44	51.2	100	36	46.5	91	40
Mean for weeks											
1-13	29.3		29.0	99		29.2	100		28.7	98	
14-52	47.4		46.4	98		47.1	99		44.6	94	
53-101	51.7		52.1	101		52.5	102		50.4	97	

Table 4
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Triethanolamine

Weeks on Study	Vehicle Control		100 mg/kg			300 mg/kg			1,000 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.8	50	19.0	101	50	19.0	101	50	19.0	101	50
2	19.4	50	19.7	102	50	19.5	101	50	20.1	104	50
3	21.0	50	21.3	101	50	21.4	102	50	21.8	104	50
4	22.5	50	22.8	101	50	23.1	103	50	23.5	104	50
5	24.0	50	24.4	102	50	24.2	101	50	24.6	103	50
6	24.4	50	24.9	102	50	24.9	102	50	25.5	105	50
7	25.1	50	25.6	102	50	25.6	102	50	26.2	104	50
8	26.2	50	26.4	101	50	26.5	101	50	27.1	103	50
9	26.6	50	27.1	102	50	27.0	102	50	27.8	105	50
10	27.5	50	28.3	103	50	28.0	102	49	28.7	104	50
11	28.3	50	29.0	103	50	28.9	102	49	29.3	104	49
12	28.8	50	29.7	103	50	29.6	103	49	30.0	104	49
13	29.6	50	30.7	104	50	30.6	103	49	31.2	105	49
17	33.3	50	35.0	105	50	34.4	103	49	35.5	107	49
21	36.2	50	37.7	104	50	36.9	102	49	38.3	106	49
25	39.0	50	40.6	104	50	40.7	104	49	41.0	105	49
29	43.0	50	44.3	103	50	43.9	102	49	44.7	104	49
33	46.3	50	47.5	103	49	47.7	103	49	47.9	104	49
37	48.8	50	49.5	101	48	49.5	101	49	50.5	104	49
41	50.8	50	51.2	101	48	51.7	102	49	52.6	104	49
45	53.9	50	54.4	101	48	54.0	100	49	54.9	102	49
49	56.0	49	55.9	100	48	55.3	99	49	56.3	101	49
53	57.3	49	56.1	98	48	56.5	99	48	57.1	100	49
57	57.4	49	56.7	99	48	56.2	98	48	57.5	100	49
61	58.3	49	58.3	100	48	57.9	99	48	58.7	101	48
65	58.6	49	58.8	100	47	59.3	101	46	60.2	103	48
69	60.2	48	59.5	99	47	60.7	101	46	60.3	100	48
73	60.5	48	60.2	100	47	60.9	101	46	61.3	101	48
77	61.3	47	60.9	99	46	61.3	100	46	61.4	100	47
81	62.7	47	59.9	96	46	60.2	96	46	60.9	97	47
85	62.1	47	58.8	95	46	60.7	98	43	60.8	98	46
89	61.8	44	59.7	97	43	60.2	97	43	60.2	97	43
93	60.3	41	58.1	96	43	58.9	98	43	58.4	97	42
97	58.2	37	54.8	94	40	56.8	98	43	55.2	95	41
101	57.1	37	56.8	100	35	55.8	98	41	54.1	95	37
Mean for weeks											
1-13	24.8		25.3	102		25.3	102		25.8	104	
14-52	45.3		46.2	102		46.0	102		46.9	104	
53-101	59.7		58.4	98		58.9	99		58.9	99	

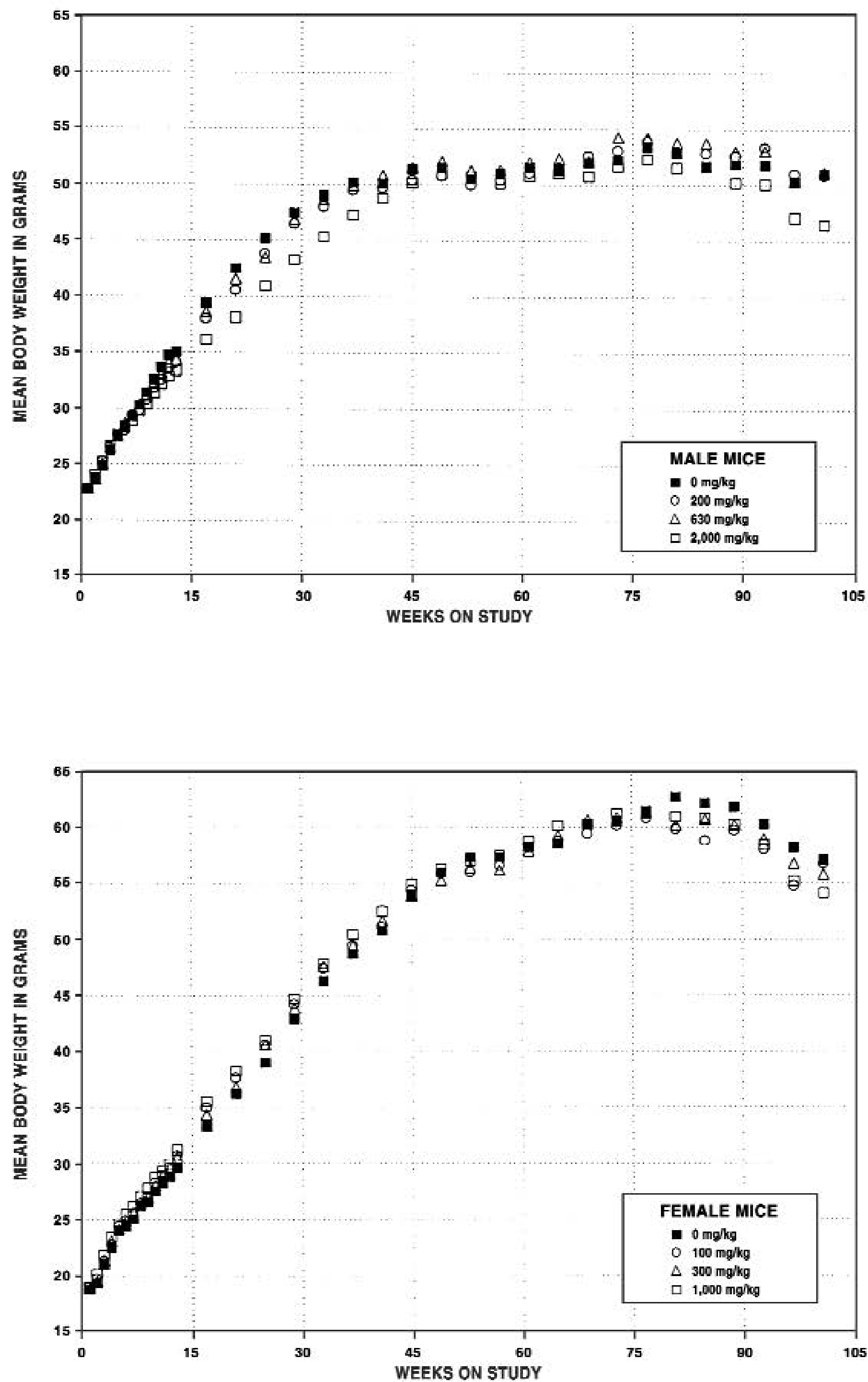


FIGURE 2
Growth Curves for Male and Female Mice Administered Triethanolamine Dermally for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver and skin. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male mice and Appendix B for female mice.

Liver: Gross lesions observed at necropsy included nodules and masses of the liver in dosed females. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends in females, and the incidences of these neoplasms in all dosed groups of females were significantly increased. The incidence of hepatocellular adenoma in 300 mg/kg females was at the upper end of the historical control range, and the incidences of hepatocelluar adenoma in 1,000 mg/kg females and of hepatocellular adenoma or carcinoma (combined) in all dosed groups of females exceeded the historical ranges in controls (all routes) given NTP-2000 diet (Tables 5, B3, and B4). The incidences of multiple hepatocellular adenoma were significantly increased in the 300 and 1,000 mg/kg females. Historically, approximately 18% (31/170) of female control mice that developed hepatocellular adenomas had multiple adenomas. In the current study, multiple adenomas did not occur in the vehicle controls; multiple adenomas occurred in 3 (17%), 7 (35%), and 17 (52%) of the females in the 100, 300, and 1,000 mg/kg groups, respectively, that developed hepatocellular adenomas.

The incidences of hepatocellular neoplasms in males were similar to those in the vehicle controls (Tables 5 and A3). The incidences of hepatoblastoma were slightly increased in 630 and 2,000 mg/kg males, but the incidences were within the historical control range and were not considered treatment-related (Tables 5, A3, and A4a). The incidence of hemangioma in 2,000 mg/kg males was greater than that in the vehicle controls, and the incidence of hemangiosarcoma in 630 mg/kg males was significantly increased; the incidences of these lesions in these groups exceeded the historical control ranges. Two 630 mg/kg males had multiple hemangiosarcomas of the liver.

Hepatocellular adenomas were nodular, expansile lesions that occupied an area greater than one liver lobule. They were well demarcated from surrounding parenchyma by a zone of compression or lack of continuity between the hepatic cords within the nodule and those of the surrounding parenchyma. There was loss of normal lobular architecture, with a lack of portal triads and haphazardly arranged hepatic cords, often with areas of atypia. Neoplastic cells were generally large, with abundant eosinophilic and variably vacuolated cytoplasm, increased nuclear to cytoplasmic ratio, and nuclear atypia and with an increased mitotic index. Hepatoblastomas are uncommon neoplasms in mice and may occur spontaneously or be chemically induced. Histologically, they have a characteristic appearance of small, dark, ovoid- to spindle-shaped cells with round to oval nuclei and scant amounts of eosinophilic cytoplasm arranged in compact sheets, islands, or trabeculae. Hepatoblastomas almost always occur within an existing proliferative lesion, most often a hepatocellular carcinoma. In NTP studies, the diagnosis of hepatoblastoma is made whenever this distinctive lesion is observed. To avoid duplicate diagnoses, no separate diagnosis is made for the lesion within which the hepatoblastoma occurs. Hemangio-sarcomas are malignant neoplasms of the vasculature, and those in the current study were characterized by pleomorphic, proliferative endothelial cells forming irregular vascular spaces, occasionally with areas of thrombosis. In contrast, hemangiomas are benign neoplasms, and those in the current study were characterized by irregular vascular spaces lined by a single layer of flattened, mature appearing endothelial cells.

Hemangiosarcoma also occurred in the spleen in two males from each of the vehicle control, 200, and 630 mg/kg groups, and the aorta of one male in the 2,000 mg/kg group (Tables 6 and A1). In one male in each of the vehicle control and dosed groups, hemangiosarcoma metastasized from the spleen or aorta to the liver, and hemangiosarcoma metastasized from the spleen to the bone marrow in one vehicle control and one 630 mg/kg male. The incidence of hemangiosarcoma in all organs was significantly increased in the 630 mg/kg group and exceeded the historical control range; this increase was attributed to the high incidence of hemangiosarcoma in the liver of mice in this group (Tables 6, A3, and A4b). Hemangiosarcoma is a malignant neoplasm of the vascular endothelium. Spontaneous hemangiosarcomas occur in 3.0% of male B6C3F_1 mice and 3.6% of females. While hemangiosarcomas may occur at a variety of sites, the liver and spleen are the

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	9	20*	31**	30**
Hemangioma[b]	0	1	0	2
Hemangiosarcoma, Multiple	0	0	2	0
Hemangiosarcoma (includes multiple)[c]				
Overall rate[d]	1/50 (2%)	0/50 (0%)	6/50 (12%)	1/50 (2%)
Adjusted rate[e]	2.1%	0.0%	13.5%	2.2%
Terminal rate[f]	1/37 (3%)	0/43 (0%)	3/34 (9%)	1/40 (3%)
First incidence (days)	726 (T)	—[h]	517	726 (T)
Poly-3 test[g]	P=0.587	P=0.501N	P=0.047	P=0.755
Hepatocellular Adenoma	19	18	23	20
Hepatocellular Carcinoma	17	14	14	11
Hepatocellular Adenoma or Carcinoma	33	27	33	25
Hepatoblastoma[i]	1	1	2	3
	Vehicle Control	**100 mg/kg**	**300 mg/kg**	**1,000 mg/kg**
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	16	22	28*	32**
Mixed Cell Focus	5	8	14*	11
Hepatocellular Adenoma, Multiple	0	3	7*	17**
Hepatocellular Adenoma (includes multiple)[j]				
Overall rate	9/50 (18%)	18/50 (36%)	20/50 (40%)	33/50 (66%)
Adjusted rate	19.9%	41.0%	43.5%	72.4%
Terminal rate	6/35 (17%)	16/34 (47%)	18/41 (44%)	25/32 (78%)
First incidence (days)	617	665	444	604
Poly-3 test	P<0.001	P=0.024	P=0.012	P<0.001
Hepatocellular Carcinoma	6	8	4	5
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	12/50 (24%)	23/50 (46%)	24/50 (48%)	34/50 (68%)
Adjusted rate	26.3%	51.0%	51.7%	74.6%
Terminal rate	7/35 (20%)	17/34 (50%)	21/41 (51%)	26/32 (81%)
First incidence (days)	595	601	444	604
Poly-3 test	P<0.001	P=0.011	P=0.009	P<0.001

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
(T) Terminal sacrifice
a Number of animals with lesion
b Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 2/1,159 (0.2% ± 0.6%), range 0%-2%
c Historical incidence: 28/1,159 (2.5% ± 1.4%), range 0%-4%
d Number of animals with neoplasm per number of animals with liver examined microscopically
e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
f Observed incidence at terminal kill
g Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.
h Not applicable; no neoplasms in animal group
i Historical incidence: 16/1,159 (1.5% ± 2.6%), range 0%-10%
j Historical incidence: 179/1,152 (16.3% ± 6.6%), range 6%-28%
k Historical incidence: 250/1,152 (22.8% ± 9.4%), range 8%-40%

Table 6
Incidences of Hemangioma and Hemangiosarcoma in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Number Necropsied	50	50	50	50
Hemangioma, Liver[a]	0	1	0	2
Hemangiosarcoma, Liver	1	0	6*	1
Hemangiosarcoma, Liver, Metastatic, Aorta	0	0	0	1
Hemangiosarcoma, Liver, Metastatic, Spleen	1	1	1	0
Hemangiosarcoma, Aorta	0	0	0	1
Hemangiosarcoma, Bone Marrow, Metastatic, Spleen	1	0	1	0
Hemangioma, Spleen	1	0	0	0
Hemangiosarcoma, Spleen	2	2	2	0
Hemangiosarcoma (All Organs)[b]				
Overall rate[c]	3/50 (6%)	2/50 (4%)	9/50 (18%)	2/50 (4%)
Adjusted rate[d]	6.3%	4.3%	20.1%	4.3%
Terminal rate[e]	1/37 (3%)	2/43 (5%)	5/34 (15%)	1/40 (3%)
First incidence (days)	624	726 (T)	517	618
Poly-3 test[f]	P=0.442N	P=0.508N	P=0.046	P=0.513N
Hemangioma or Hemangiosarcoma (All Organs)[g]				
Overall rate	4/50 (8%)	3/50 (6%)	9/50 (18%)	4/50 (8%)
Adjusted rate	8.4%	6.4%	20.1%	8.6%
Terminal rate	2/37 (5%)	3/43 (7%)	5/34 (15%)	3/40 (8%)
First incidence (days)	624	726 (T)	517	618
Poly-3 test	P=0.550	P=0.509N	P=0.092	P=0.628

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 59/1,159 (5.3% ± 3.4%), range 0%-14%
[c] Number of animals with neoplasm per number of animals necropsied
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.
[g] Historical incidence: 73/1,159 (6.4% ± 3.3%), range 2%-14%

most common sites in male B6C3F$_1$ mice, and the spleen and subcutis are the most common sites in females (Chandra, S.A., Hardisty, J.F., Seely, J.C., Haseman, J.K., and Maronpot, R.R., unpublished). In 20 chemical studies for which there was a chemical-related increased incidence in vascular neoplasms, the increased incidences occurred most commonly at a specific site, and less commonly at two or more specific sites. In general, the vasculature as a whole is not affected; rather the vasculature within a specific organ/tissue is affected. The most common site of chemically induced vascular neoplasms in NTP studies is the liver.

In the current study, the incidences at individual sites and all sites combined are presented in the results. Only the incidence in the liver stands out as being statistically significant and/or outside of historical control ranges, and only in the 630 mg/kg group. The incidences of hemangioma of the liver were low in each group and not significantly different between groups, although they did exceed historical control ranges. When interpreting potential treatment-related incidences of many neoplasm types, the combined incidence of the benign and malignant forms is an important consideration. However, unlike the liver and kidney, for example, where there is evidence of a morphological and biological continuum between benign and malignant neoplasms, the link between hemangioma and hemangiosarcoma is not as strong. Also, the majority of NTP studies with chemical-related increases in the incidences of vasculature neoplasms have involved hemangiosarcomas without an increase in hemangiomas. However, there are exceptions.

The incidences of eosinophilic focus in all dosed groups of males and in 300 and 1,000 mg/kg females were significantly increased (Tables 5, A5, and B5). The incidences of mixed cell focus in dosed groups of females were greater than that in the vehicle controls, and the incidence in the 300 mg/kg group was significantly increased (Tables 5 and B5). Foci of cellular alteration were sharply demarcated clusters of cells with altered cytoplasmic tinctoral properties. Eosinophilic and mixed foci were variably sized and ranged from approximately one hepatic lobule to several hepatic lobules, generally causing little compression of the adjacent parenchyma. There was little or no alteration of normal hepatic architecture within the focus, and cellular atypia was generally absent. Component cells of the eosinophilic foci were large with abundant eosinophilic cytoplasm. In the mixed foci, the eosinophilic cells were admixed with a second population of cells with prominent fine to coarse cytoplasmic vacuolation.

Skin: Gross lesions observed at necropsy included visible crusts at the site of application in all dosed groups of mice, and more lesions occurred in 630 and 2,000 mg/kg males. Treatment-related epidermal hyperplasia, suppurative inflammation, and ulceration and dermal chronic inflammation occurred at the site of application in most dosed groups of mice, and the incidences and severities of these lesions generally increased with increasing dose (Tables 7, A5, and B5). Epidermal hyperplasia varied from minimal to moderate in males and minimal to mild in females. Moderate hyperplasia in males was characterized by rete peg formation and an epidermal thickness approximately six times the normal thickness. Epidermal suppurative inflammation generally occurred in conjunction with the epidermal hyperplasia and consisted of heavy, focal aggregations of viable and degenerate neutrophils, predominantly within or superficial to the stratum corneum (superficial intracorneal pustule formation). Aggregates superficial to the stratum corneum also occurred and were admixed with keratin and proteinaceous material (serocellular crusts). Ulcers were less common and were characterized by complete necrosis of the epidermis, variable subjacent dermal erosion and associated chronic inflammatory cell infiltration and fibroplasia. Ulcers were covered with serocellular crusts comprising cellular debris, keratin, fibrin, and inflammatory cells. Chronic inflammation of the dermis occurred in association with areas of epidermal hyperplasia and/or ulceration. It consisted of focal and more diffuse, loose aggregates of mixed inflammatory cells (neutrophils, eosinophils, mast cells, lymphoctes and plasma cells), often admixed with areas of active fibroblasts aligned parallel to the surface of the skin.

Absorption, Distribution, Metabolism, and Excretion Studies

Data for the disposition of a 3 mg/kg intravenous dose of [^{14}C]-triethanolamine female rats are presented in Table G1. The radioactivity was rapidly excreted in the urine, and 90% of the dosed radioactivity was recovered in the urine within 24 hours. An average of 98% of the dose was recovered in the urine within 72 hours after dosing, and approximately 0.6% of the radioactivity was recovered in the feces during this time. Less than 0.5% of the dose was recovered in carbon dioxide traps, and less than 0.1% was recovered in volatiles traps.

Table 7
Incidences of Nonneoplastic Lesions of the Skin (Site of Application) in Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Epidermis, Hyperplasia[a]	5 (1.2)[b]	44** (1.5)	45** (2.0)	49** (2.7)
Epidermis, Inflammation, Suppurative	1 (1.0)	11** (1.5)	33** (1.7)	42** (2.8)
Epidermis, Ulcer	0	3 (1.0)	20** (1.4)	47** (2.6)
Dermis, Inflammation, Chronic	1 (1.0)	15** (1.1)	40** (1.6)	49** (2.5)
	Vehicle Control	**100 mg/kg**	**300 mg/kg**	**1,000 mg/kg**
Female				
Number Examined Microscopically	50	50	50	50
Epidermis, Hyperplasia	14 (1.3)	50** (1.9)	46** (2.0)	50** (2.0)
Epidermis, Inflammation, Suppurative	1 (2.0)	2 (2.0)	20** (1.5)	32** (2.2)
Epidermis, Ulcer	1 (3.0)	1 (3.0)	6 (1.5)	17** (1.6)
Dermis, Inflammation, Chronic	4 (1.8)	27** (1.1)	31** (1.6)	44** (1.8)

** Significantly different ($P \leq 0.01$) from the vehicle control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

The distribution of radioactivity from female rats following intravenous administration of [^{14}C]-triethanolamine is presented in Table G2. Only 0.9% of the dose remained in the tissues 72 hours after dosing. In contrast to diethanolamine, which was only slowly excreted (30% of dose within 48 hours) and accumulated in the brain, heart, kidney, spleen (5% of dose at 48 hours), and liver (27% of dose at 48 hours) in a process thought to involve biochemical mimicry with the natural alkanolamine ethanolamine (Mathews *et al*., 1995), comparatively little triethanol-amine bioaccumulated in the tissues.

Data for the excretion of radioactivity following dermal administration of 68 and 276 mg/kg [^{14}C]-triethanolamine in female rats is presented in Table G3, and the distribution of radioactivity present in tissues 72 hours after dosing is presented in Table G4. Approximately 20% to 30% of the dose was absorbed within 72 hours following dermal exposure. The mean percentage of dose absorbed increased with increasing dose, but the increase was not statistically significant (Table G5).

The disposition of a 3 mg/kg intravenous dose of [^{14}C]-triethanolamine in female mice is presented in Table G6. With only 40% of the dose excreted within 24 hours, mice appeared to excrete intravenously administered triethanolamine more slowly than did rats. Considerably more of the dose was recovered in the feces of mice (28%) than in rats (0.6%). However, it is common for mice to shred and powder their food pellets, and the feces collections are often contaminated with urine-soaked solids. Less than 0.5% of the dose was recovered in carbon dioxide traps, and less than 0.1% was recovered in volatiles traps.

The distribution of radioactivity in tissue samples from female mice is presented in Table G7. As was the case for rats, the heart, kidney, liver, lung, and spleen contained higher concentrations of triethanolamine equivalents relative to blood.

Mice absorbed dermally applied triethanolamine more readily than did rats (Tables G8 and G9) and excreted the absorbed radioactivity in the urine and feces (which were probably contaminated with the urine as noted above), with 28% to 48% of the dose recovered in excreta within 24 hours. The percentage of the dose absorbed increased with increasing dose.

Urine collected 6 to 24 hours after intravenous dosing and 48 to 72 hours after dermal application of triethanolamine in female rats was analyzed by HPLC (Figure G1). The chromatogram contains a peak that coelutes with triethanolamine and two other peaks that comprise about 5% of the radioactivity in the sample. These peaks, however, were also present in the chromatogram of the radiolabeled test article and may reflect the presence of impurities rather than metabolites. The metabolite fractions were collected and incubated with purified β-glucuronidase, as was an aliquot of the whole urine. Analysis of these samples showed no change in the metabolite profile. Similarly, urine collected 6 to 24 hours after intravenous or dermal dosing contained more than 95% radiolabeled components that coeluted with unchanged triethanolamine, with minor components eluting the same fractions in mice as those in rats.

Genetic Toxicology

Triethanolamine (33 to 3,333 µg/plate) was negative for induction of mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with or without S9 metabolic activation (Table C1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary cells, no induction of sister chromatid exchanges (SCEs) (Table C2) or chromosomal aberrations (Abs) (Table C3) was observed with or without S9 (Galloway *et al.*, 1987). In the SCE test without S9, the first of two trials was negative. In the second trial, a significant increase in SCEs was observed at the highest dose tested (2,520 µg/mL), but the trend test was negative ($P \geq 0.025$), and the trial was concluded to be equivocal. Severe cytotoxicity limited the number of cells that could be scored at this dose. Overall, the SCE test was considered to be negative. Cytotoxicity was also noted at the highest dose tested (4,030 µg/mL) in the Abs test without S9.

Triethanolamine administered by feeding or injection at doses up to 30,000 ppm did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Table C4; Yoon *et al.*, 1985). Results of an *in vivo* peripheral blood micronucleus test in mice were also negative (Table C5; Witt *et al.*, 2000). In this test, blood samples were obtained from male and female mice after 13 weeks of dermal applications of 1,000 to 4,000 mg/kg triethanolamine. No significant increases in the frequencies of micronucleated normochromatic erythrocytes were observed at any dose level, and the percentages of polychromatic erythrocytes in the dosed groups were similar to those in the vehicle control groups, indicating an absence of bone marrow toxicity.

DISCUSSION AND CONCLUSIONS

The National Cancer Institute nominated triethanolamine for evaluation of its safety and potential carcinogenicity due to its widespread use in cosmetics and other consumer products. In 1999, the National Toxicology Program completed and published the results of 3-month and 2-year studies in F344/N rats and B6C3F$_1$ mice administered topical applications of triethanolamine (NTP, 1999). The 2-year F344/N rat study indicated equivocal evidence of carcinogenic activity in males based on a marginal increase in the incidence of renal tubule cell adenoma. No evidence of carcinogenic activity was found in female rats. Treated male and female B6C3F$_1$ mice developed liver neoplasms; however, male mice had a pattern of nonneoplastic liver lesions (hepatitis) along with microscopic silver-staining helical organisms within the liver, which suggested an infection with *Helicobacter hepaticus.* Polymerase chain reaction (PCR) based assays and culture confirmed infection in male and female mice even though females had no evidence of *H. hepaticus*-associated hepatitis. Increases in the incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al*., 1994; Fox *et al*., 1996; Hailey *et al*., 1998). Therefore, the NTP proposed that the male mouse study be considered inadequate. Because there was no evidence that females had *H. hepaticus*-associated hepatitis, the female mouse study was interpreted as showing some evidence of carcinogenic activity based on an increase in hepatocellular neoplasms. However, the NTP Board of Scientific Counselors Technical Reports Review Subcommittee considered the entire mouse study to be inadequate because of uncertainty about the potential for *H. hepaticus* infection to influence the liver tumor response to triethanolamine.

Due to the uncertainty about the potential of *H. hepaticus* to influence the incidence of liver neoplasms in B6C3F$_1$ mice, the NTP decided to repeat the 2-year study. With the exception of the diet, the design of the preceding study including route of administration, dose selection, and treatment duration was preserved in the present study with the purpose of reproducing as closely as possible the exposure conditions used previously. The NTP-2000 diet was used in the current study, replacing the NIH-07 diet used in the previous study. This new diet has been used in all NTP studies since 1994, and composition and performance data have been published (Rao, *et al.*, 1997).

Following detection of the *H. hepaticus* infection in 12 NTP studies (Hailey *et al*., 1998), the breeding colony was rederived and was determined to be free of infection. Also, in order to assure that animals of the repeat triethanolamine study were not infected with *H. hepaticus,* sentinel animals, as well as four male and five female mice from the study groups were analyzed for *H. hepaticus* infection at 18 months. PCR of fecal pellets, serology, and bacteriological cultures found no evidence of *H. hepaticus* in any of the animals evaluated (Appendix F).

In general, results reported here are consistent with those reported in NTP Technical Report 449 on triethanolamine (NTP, 1999). Treatment did not affect survival of animals of either sex after 104 weeks of exposure. Similar to the previous study, treatment-related effects on body weights of dosed mice were observed only in males in the highest dosed group by the end of the study. However, body weights of the animals used in this study were higher than those of the mice in the previous study (approximately 20% in females and 5% in males).

Consistent with the first study (NTP, 1999), female mice in the current study again showed an increase in the incidences of hepatocellular neoplasms. In the current study, increased incidences of hepatocellular adenomas and multiple hepatocelluar adenomas were observed in all dosed groups of females (in contrast to the first study where this was a high-dose effect only), and the incidences in the dosed groups exceeded the upper historical control incidence. The primary difference in the liver neoplasm incidences between the two triethanolamine studies was in the control groups, with the first study showing a control rate greater than twice the control incidence seen in the second study. This may be associated with the change from the use of the NIH-07 diet to the NTP-2000 diet in the intervening period. In that

respect, Rao and Crockett (2003) demonstrated that female B6C3F_1 mice fed the NTP-2000 diet have markedly ($P<0.01$) reduced liver neoplasm rates compared to female mice fed the NIH-07 diet (14.3% versus 34.2% for dosed feed studies). This was in part attributed to a reduction in average body weight of mice fed the NTP-2000 diet. However, a reduction in liver neoplasms in control mice in inhalation studies was also noted using the NTP-2000 diet, and this occurred without a concurrent reduction in body weight.

Application of a prediction model derived by Haseman *et al.* (1997) indicates that the control liver tumor incidence of 46% in the first study (NTP, 1999) was very similar to what would be expected for individually housed control B6C3F_1 mice of equivalent age and body weight fed the NIH-07 diet (42%). Using this same approach and the historical control data for the 21 NTP studies that have used the NTP-2000 diet, a regression analysis was carried out to determine the best fitting model relating liver tumor occurrence to 2-year survival and 1-year body weight. This model was then applied to the data in the current study to determine if the observed control tumor rates were consistent with this model. The observed and predicted liver tumor rates were similar for both liver adenoma (19% predicted, 18% observed) and liver adenoma or carcinoma (combined) (27% predicted, 24% observed). Thus, the control liver tumor incidences in this study were essentially those expected in control animals of this size and longevity. Based on this, it appears likely that diet was the primary factor responsible for the difference in the liver tumor rates between the control groups of the two studies.

A significant increase in the incidences of multiple hepatocellular adenomas were also observed in treated female mice with adenomas in the current study (35% and 52% in the 300 and 1,000 mg/kg groups, respectively). Historically, approximately 18% of female control mice fed the NTP-2000 diet that developed hepatocellular adenomas had multiple adenomas. None of the nine adenomas observed in the control group were multiple, and the proportion of hepatocellular adenomas that were multiple showed a clear dose-response trend.

Treated animals of both sexes also developed significant increases in eosinophilic foci in the liver in all dosed groups. Compared to the previous study, the overall incidence of this lesion in females was about two times the incidence reported in the 1999 study. However, taken together, incidences of hepatocellular adenomas and eosinophilic foci result in a rate of proliferative hepatic lesions that is reasonably similar in the two studies.

Male mice receiving 630 mg/kg triethanolamine developed an increased incidence of hemangiosarcoma that exceeded the historical control range. Similar to other chemical-related vascular tumors observed in previous NTP studies, the liver was the organ with the highest incidence of hemangiosarcoma. However, there was no increase in the next dose group (2,000 mg/kg), or in any of the dosed groups of females, nor was there an increase in the incidence of these tumors in the previous study. Therefore, the association between triethanolamine and hemangiosarcoma of the liver was considered an uncertain finding.

A major difference between the results of previous and current NTP triethanolamine studies was the unexpected disparity in skin response to the application of triethanolamine. Because of this discrepancy, records from both studies were evaluated to determine if any differences in the chemical (dose formulation or preparation), administration of the chemical, animal preparation (clipping, etc.) and/or handling of the animals could explain the different response. The formalin-fixed skin from the site of application of several animals from the original study was reevaluated to determine if lesions had been missed. None of these evaluations revealed any information that could explain the differences in the local effect. Although lesions were qualitatively similar, males were more severely affected in the current study.

Based on the microscopic diagnoses, the changes in the skin at the site of application appear fairly severe, particularly in males. However, the gross evaluation indicated that the ulcerative lesions were small, focal to multifocal, affecting a relatively small portion of the skin at the site of application. In this study, as in all skin paint studies, a routine section of skin was taken from a specific area of the site of application. Additional sections were taken of grossly observed lesions, which in this study generally consisted of small focal crusty areas. Microscopically, the ulcers were most commonly identified within the crusty areas from the additional sections, and not from the routine section. Also, in general, the most severe suppurative inflammation and hyperplasia were associated with existing and/or healing ulcers, particularly in females. The lesions in the skin were not considered sufficiently severe to require early termination of affected animals.

Males appeared to be more sensitive to the local effects of triethanolamine, although the major treatment-related response outside the skin at the site of application was the increased incidence of hepatocellular adenomas seen in females. However, in females, both incidence and severity of the skin lesions, and the incidence of hepatocellular adenomas appeared to increase with increasing dose. Therefore, there was a concern that enhanced absorption across lesioned skin at the site of application might have played a role in some female mice, predisposing those animals to develop hepatocellular adenomas.

In order to address this concern, logistic regression procedures were used to determine the relative importance of these two factors (incidence and severity of skin lesions) in the prediction of liver tumor occurrence. The severities of the following skin lesions were considered: epidermal hyperplasia, suppurative inflammation, and ulceration and dermal chronic inflammation. The summed severities of these four lesions were also evaluated. Logistic regression analysis revealed that while the occurrence of chronic dermal inflammation was significantly ($P<0.05$) correlated with the occurrence of liver neoplasms, the increasing trend in liver neoplasm incidence due to triethanolamine remained significant ($P<0.05$) even after adjusting for the possible influence of dermal chronic inflammation. Thus, the increased incidences of liver neoplasms observed in female mice receiving triethanolamine cannot be attributed solely to the concurrently observed increase in nonneoplastic skin lesions at the site of application.

Finally, increased incidences of malignant lymphoma reported previously in female ICL-JCR mice treated with 0.03% or 0.3% of triethanolamine in the diet (Hoshino and Tanooka, 1978) raised concerns regarding the carcinogenic potential of triethanolamine. However, a treatment-related increase in the incidence of malignant lymphoma in B6C3F$_1$ mice was not identified in the current or the previous NTP (1999) study.

Results from the current study demonstrated that chronic administration of triethanolamine does not significantly affect the hepatic carcinoma rates in B6C3F$_1$ mice. Although hepatocellular adenoma is a common benign tumor that occurs with variable incidence in female B6C3F$_1$ mice, the dose-related increases in the incidences of hepatocellular adenomas and multiple hepatocellular adenomas described in this report constitute some evidence of carcinogenic activity of triethanolamine in female B6C3F$_1$ mice. Potential mechanisms accounting for this fact will require further study.

Conclusions

Under the conditions of this 2-year dermal study, there was *equivocal evidence of carcinogenic activity** of triethanolamine in male B6C3F$_1$ mice based on the occurrence of liver hemangiosarcoma. There was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of hepatocellular adenoma.

Exposure to triethanolamine by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related nonneoplastic lesions at the site of application.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DERMAL STUDY OF TRIETHANOLAMINE

TABLE A1 Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine 50

TABLE A2 Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine 54

TABLE A3 Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine 78

TABLE A4a Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice 81

TABLE A4b Historical Incidence of Hemangioma or Hemangiosarcoma (All Organs) in Control Male B6C3F$_1$ Mice 82

TABLE A5 Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine 83

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine[a]

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	5	2	6	8
Natural deaths	8	5	10	2
Survivors				
Terminal sacrifice	37	43	34	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma	2 (4%)	1 (2%)		1 (2%)
Carcinoma, multiple	1 (2%)			
Sarcoma, metastatic, adrenal medulla		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Hemangioma		1 (2%)		2 (4%)
Hemangiosarcoma	1 (2%)		4 (8%)	1 (2%)
Hemangiosarcoma, multiple			2 (4%)	
Hemangiosarcoma, metastatic, blood vessel				1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)	1 (2%)	1 (2%)	
Hepatoblastoma	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	11 (22%)	10 (20%)	13 (26%)	10 (20%)
Hepatocellular carcinoma, multiple	6 (12%)	4 (8%)	1 (2%)	1 (2%)
Hepatocellular adenoma	13 (26%)	14 (28%)	12 (24%)	15 (30%)
Hepatocellular adenoma, multiple	6 (12%)	4 (8%)	11 (22%)	5 (10%)
Hepatocholangiocarcinoma				1 (2%)
Histiocytic sarcoma		1 (2%)		2 (4%)
Sarcoma, metastatic, adrenal medulla		1 (2%)		
Mesentery	(3)	(3)	(5)	(7)
Fibrous histiocytoma				1 (14%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)		1 (2%)
Tongue				(1)
Squamous cell carcinoma				1 (100%)
Tooth	(19)	(18)	(14)	(13)
Odontoma	1 (5%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, hemangiosarcoma				1 (2%)
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Histiocytic sarcoma				1 (2%)

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Subcapsular, adenoma	3 (6%)	3 (6%)	6 (12%)	5 (10%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	1 (2%)			1 (2%)
Sarcoma		1 (2%)		
Pituitary gland	(50)	(49)	(49)	(50)
Pars distalis, adenoma			1 (2%)	
Pars intermedia, adenoma	1 (2%)			1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
Follicle, adenoma	1 (2%)		1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, spleen	1 (2%)		1 (2%)	
Histiocytic sarcoma				1 (2%)
Lymph node	(1)		(1)	(1)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (100%)			
Mediastinal, fibrous histiocytoma, metastatic, mesentery				1 (100%)
Mediastinal, hepatocellular carcinoma, metastatic, liver			1 (100%)	
Pancreatic, fibrous histiocytoma, metastatic, mesentery				1 (100%)
Renal, fibrous histiocytoma				1 (100%)
Lymph node, mesenteric	(50)	(48)	(48)	(50)
Histiocytic sarcoma				1 (2%)
Spleen	(49)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)	2 (4%)	2 (4%)	
Histiocytic sarcoma		1 (2%)		1 (2%)
Thymus	(48)	(47)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, hibernoma				1 (2%)
Subcutaneous tissue, melanoma malignant	1 (2%)			
Subcutaneous tissue, skin, site of application, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, site of application, dermis, mast cell tumor benign		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	6 (12%)	11 (22%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	6 (12%)	6 (12%)	8 (16%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			1 (2%)
Carcinoma, metastatic, harderian gland		1 (2%)		
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hepatoblastoma, metastatic, liver			1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	8 (16%)	6 (12%)	6 (12%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		2 (4%)
Special Senses System				
Harderian gland	(50)	(50)	(49)	(50)
Adenoma	6 (12%)	2 (4%)	2 (4%)	5 (10%)
Carcinoma		1 (2%)		1 (2%)
Bilateral, adenoma	1 (2%)			1 (2%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Renal tubule, adenoma	1 (2%)		1 (2%)	1 (2%)
Renal tubule, carcinoma, multiple				1 (2%)

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		2 (4%)
Lymphoma malignant			1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	35	43	41
Total primary neoplasms	75	62	80	79
Total animals with benign neoplasms	30	25	32	32
Total benign neoplasms	42	35	46	48
Total animals with malignant neoplasms	28	24	27	21
Total malignant neoplasms	33	27	34	31
Total animals with metastatic neoplasms	10	8	9	6
Total metastatic neoplasms	11	10	12	14

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	511	580	624	628	664	684	684	688	694	714	716	725	725	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	023	006	050	034	003	022	029	011	030	009	010	021	047	007	012	015	016	018	019	028	031	035	040	042	046
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, multiple																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, spleen			X																						
Hepatoblastoma																									
Hepatocellular carcinoma	X	X		X	X	X										X			X	X					X
Hepatocellular carcinoma, multiple							X		X	X		X												X	
Hepatocellular adenoma																			X	X	X				
Hepatocellular adenoma, multiple								X	X						X										
Mesentery														+			+					+			
Oral mucosa		+			+		+		+		+	+			+	+	+		+	+	+		+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+						+		+	+	+	+	+						+	+			
Odontoma														X											
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																						X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma																X									

+: Tissue examined microscopically M: Missing tissue X: Lesion present
A: Autolysis precludes examination I: Insufficient tissue Blank: Not examined

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	8	8	8	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
	0	0	0	0	1	2	2	2	2	3	3	3	3	4	4	0	1	1	2	3	3	4	4	4	4	Tissues/
	1	4	5	8	4	0	5	6	7	2	3	6	8	4	5	2	3	7	4	7	9	1	3	8	9	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X					X																			2
Carcinoma, multiple																					X					1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Hemangiosarcoma, metastatic, spleen																										1
Hepatoblastoma									X																	1
Hepatocellular carcinoma	X			X																						11
Hepatocellular carcinoma, multiple																		X								6
Hepatocellular adenoma							X	X	X	X		X		X			X		X	X			X			13
Hepatocellular adenoma, multiple		X				X																X				6
Mesentery																										3
Oral mucosa	+		+	+	+	+	+		+	+	+			+		+			+	+		+	+	+		31
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+		+		+		+		+	+		+		+		+		+							19
Odontoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma											X				X											3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign											X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars intermedia, adenoma								X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenoma																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	511	580	624	628	664	684	684	688	694	714	716	725	725	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	023	056	050	034	003	022	029	011	030	009	010	021	047	007	012	015	016	018	019	028	031	035	040	042	046
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen			X																						
Lymph node	+																								
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma			X					X																	
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, melanoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma	X																	X							X
Alveolar/bronchiolar carcinoma, multiple					X																				
Hepatocellular carcinoma, metastatic, liver		X				X	X		X	X		X				X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	001	004	005	008	014	020	025	026	027	032	033	036	038	044	045	002	013	017	024	037	039	041	043	048	049	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Lymph node																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																							X			1
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, melanoma malignant	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X													X					X			X	X	6
Alveolar/bronchiolar carcinoma				X											X	X										6
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																		X								8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	511	580	624	628	664	684	684	688	694	714	716	725	725	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	023	056	050	034	003	022	029	011	030	009	010	021	047	007	012	015	016	018	019	028	031	035	040	042	046
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																				X				
Bilateral, adenoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma															X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	001	004	005	008	014	020	025	026	027	032	033	036	038	044	045	002	013	017	024	037	039	041	043	048	049	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X	X				X			X		6
Bilateral, adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

Number of Days on Study	334	502	554	615	637	676	710	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	057	083	058	074	062	071	085	054	059	063	068	073	077	078	079	080	081	082	084	087	095	096	097	098	099
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Sarcoma, metastatic, adrenal medulla					X																				
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Hemangiosarcoma, metastatic, spleen																									
Hepatoblastoma																									
Hepatocellular carcinoma				X							X							X							
Hepatocellular carcinoma, multiple			X		X																	X			
Hepatocellular adenoma								X			X						X	X							
Hepatocellular adenoma, multiple																X				X					
Histiocytic sarcoma							X																		
Sarcoma, metastatic, adrenal medulla					X																				
Mesentery								+																	
Oral mucosa									+		+		+			+	+	+				+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X			X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+	+	+			+	+	+		+							+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

Number of Days on Study	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 0 0	0 5 1	0 5 2	0 5 3	0 5 5	0 6 0	0 6 4	0 6 5	0 6 7	0 6 9	0 7 5	0 7 6	0 8 6	0 8 8	0 9 0	0 9 3	0 9 4	0 5 6	0 6 1	0 6 6	0 7 0	0 7 2	0 8 9	0 9 1	0 9 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Sarcoma, metastatic, adrenal medulla																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma, metastatic, spleen		X																								1
Hepatoblastoma				X																						1
Hepatocellular carcinoma	X	X									X	X			X								X		X	10
Hepatocellular carcinoma, multiple																					X					4
Hepatocellular adenoma	X	X	X	X			X	X	X	X			X											X		14
Hepatocellular adenoma, multiple											X								X							4
Histiocytic sarcoma																										1
Sarcoma, metastatic, adrenal medulla																										1
Mesentery												+										+				3
Oral mucosa			+	+	+	+	+	+		+	+	+	+	+	+	+		+		+	+	+	+	+		26
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+		+	+			+									+	+			+		+			+	18
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma									X																X	3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

Number of Days on Study	334	502	554	615	637	676	710	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	057	083	058	074	062	071	085	054	059	063	068	073	077	078	079	080	081	082	084	087	095	096	097	098	099
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma							X																		
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, site of application, dermis, mast cell tumor benign																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X								X		X							
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																							X		
Carcinoma, metastatic, harderian gland																				X					
Hepatocellular carcinoma, metastatic, liver			X	X	X						X											X			
Histiocytic sarcoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																				X					

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

Number of Days on Study	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 0 0	0 5 1	0 5 2	0 5 3	0 5 5	0 6 0	0 6 4	0 6 5	0 6 7	0 6 9	0 7 5	0 7 6	0 8 6	0 8 8	0 9 0	0 9 3	0 9 4	0 5 6	0 6 1	0 6 6	0 7 0	0 7 2	0 8 9	0 9 1	0 9 2	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																					X					1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																						X		2
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	47
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, site of application, dermis, mast cell tumor benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X					X	X																			6
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar carcinoma										X			X					X				X		X		6
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver															X											6
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X															X								2
Carcinoma																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

	3	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	0	5	1	3	7	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	4	2	4	5	7	6	0	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	5	8	5	7	6	7	8	5	5	6	6	7	7	7	7	8	8	8	8	8	9	9	9	9	9
	7	3	8	4	2	1	5	4	9	3	8	3	7	8	9	0	1	2	4	7	5	6	7	8	9
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	
Carcass ID Number	100	051	052	053	055	060	064	065	067	069	075	076	086	088	090	093	094	056	061	066	070	072	089	091	092	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

Number of Days on Study	439	443	486	487	503	517	566	603	614	659	673	676	691	699	705	708	726	726	726	726	726	726	726	726	726
Carcass ID Number	124	118	117	104	110	112	120	146	125	115	132	138	119	134	141	128	103	105	107	108	121	123	127	130	133
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X													X						
Hemangiosarcoma, multiple									X							X									
Hemangiosarcoma, metastatic, spleen										X															
Hepatoblastoma																									X
Hepatocellular carcinoma	X			X	X	X							X	X	X	X	X	X				X			X
Hepatocellular carcinoma, multiple			X																						
Hepatocellular adenoma										X							X			X	X	X	X		
Hepatocellular adenoma, multiple											X		X						X					X	
Mesentery																		+						+	
Oral mucosa	+	+			+			+		+				+	+		+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+		+						+		+		+				+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Subcapsular, adenoma												X				X		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	+	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma																			X						
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

Number of Days on Study	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 3 6	1 4 5	1 0 1	1 0 2	1 0 6	1 1 4	1 1 6	1 3 5	1 3 7	1 3 9	1 4 2	1 4 3	1 4 4	1 4 7	1 4 8	1 4 9	1 5 0	1 0 9	1 1 1	1 1 3	1 2 2	1 2 6	1 2 9	1 3 1	1 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																				X	4
Hemangiosarcoma, multiple																										2
Hemangiosarcoma, metastatic, spleen																										1
Hepatoblastoma							X																			2
Hepatocellular carcinoma																									X	13
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma					X						X			X				X			X			X		12
Hepatocellular adenoma, multiple	X								X			X							X	X		X			X	11
Mesentery					+														+			+				5
Oral mucosa	+	+		+	+	+	+	+	+	+	+	+	+	+		+				+	+		+	+	+	35
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth									+			+				+	+	+	+			+			+	14
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Subcapsular, adenoma	X						X		X																	6
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	39
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicle, adenoma																										1
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

Number of Days on Study	439	443	486	487	503	517	566	603	614	659	673	676	691	699	705	708	726	726	726	726	726	726	726	726	726
Carcass ID Number	124	118	117	104	110	112	120	146	125	115	132	138	119	134	141	128	103	105	107	108	121	123	127	130	133
Genital System																									
Coagulating gland																+									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen										X															
Lymph node													+												
Mediastinal, hepatocellular carcinoma, metastatic, liver													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, skin, site of application, hemangiosarcoma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X					X			X		X	X		X								
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma					X		X	X																	
Hepatoblastoma, metastatic, liver																									X
Hepatocellular carcinoma, metastatic, liver	X				X								X			X	X	X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

Number of Days on Study	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	
Carcass ID Number	136	145	101	102	106	114	116	135	137	139	142	143	144	147	148	149	150	109	111	113	122	126	129	131	140	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Lymph node																										1
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X									2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, skin, site of application, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X	X				X		X							X	11
Alveolar/bronchiolar adenoma, multiple																			X							1
Alveolar/bronchiolar carcinoma	X			X						X					X										X	8
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	2

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

	4	4	4	4	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	4	8	8	0	1	6	0	1	5	7	7	9	9	0	0	2	2	2	2	2	2	2	2	2
	9	3	6	7	3	7	6	3	4	9	3	6	1	9	5	8	6	6	6	6	6	6	6	6	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	2	1	1	0	1	1	2	4	2	1	3	3	1	3	4	2	0	0	0	0	2	2	2	3	3
	4	8	7	4	0	2	0	6	5	5	2	8	9	4	1	8	3	5	7	8	1	3	7	0	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																	X								

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg

Number of Days on Study	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	
Carcass ID Number	136	145	101	102	106	114	116	135	137	139	142	143	144	147	148	149	150	109	111	113	122	126	129	131	140	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	399	554	566	572	618	628	644	683	684	684	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	168	185	183	171	196	176	161	186	152	172	153	155	156	157	163	164	165	173	174	175	178	179	180	181	188
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																								
Carcinoma																									X
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																			X						
Hemangiosarcoma																X									
Hemangiosarcoma, metastatic, blood vessel					X																				
Hepatoblastoma					X														X						
Hepatocellular carcinoma				X				X						X		X			X	X					
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma					X	X					X						X			X			X		X
Hepatocellular adenoma, multiple														X				X	X						
Hepatocholangiocarcinoma			X																						
Histiocytic sarcoma									X			X													
Mesentery	+		+												+				+						
Fibrous histiocytoma			X																						
Oral mucosa			+					+	+							+	+			+	+	+	+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Tooth							+		+		+						+			+			+	+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aorta, hemangiosarcoma					X																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney								X																	
Fibrous histiocytoma, metastatic, mesentery			X																						
Histiocytic sarcoma												X													

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	
Carcass ID Number	191	193	199	151	159	160	162	169	170	182	184	187	194	195	197	198	154	158	166	167	177	189	190	192	200	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma											X															2
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, blood vessel																										1
Hepatoblastoma																							X			3
Hepatocellular carcinoma		X										X	X							X						10
Hepatocellular carcinoma, multiple				X																						1
Hepatocellular adenoma		X							X			X	X		X		X	X						X		15
Hepatocellular adenoma, multiple					X														X							5
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										2
Mesentery								+	+												+					7
Fibrous histiocytoma																										1
Oral mucosa	+	+	+	+	+		+	+	+	+		+	+	+		+	+	+	+	+	+			+	+	30
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+																							1
Squamous cell carcinoma			X																							1
Tooth								+			+	+					+					+			+	13
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Aorta, hemangiosarcoma																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Fibrous histiocytoma, metastatic, mesentery																										1
Histiocytic sarcoma																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	399	554	566	572	618	628	644	683	684	684	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	168	185	183	171	196	176	161	186	152	172	153	155	156	157	163	164	165	173	174	175	178	179	180	181	188
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma					X														X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma		X																							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery			X																						
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymph node			+																						
Mediastinal, fibrous histiocytoma, metastatic, mesentery			X																						
Pancreatic, fibrous histiocytoma, metastatic, mesentery			X																						
Renal, fibrous histiocytoma			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney								X																	
Fibrous histiocytoma, metastatic, mesentery			X																						
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma										X															
Subcutaneous tissue, hibernoma								X																	

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	
Carcass ID Number	191	193	199	151	159	160	162	169	170	182	184	187	194	195	197	198	154	158	166	167	177	189	190	192	200	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma			X											X			X									5
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Coagulating gland						+																				1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																										1
Mediastinal, fibrous histiocytoma, metastatic, mesentery																										1
Pancreatic, fibrous histiocytoma, metastatic, mesentery																										1
Renal, fibrous histiocytoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney																										1
Fibrous histiocytoma, metastatic, mesentery																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, hibernoma																										1

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	399	554	566	572	618	628	644	683	684	684	726	726	726	726	726	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	168	185	183	171	196	176	161	186	152	172	153	155	156	157	163	164	165	173	174	175	178	179	180	181	188
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X				X	X						
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, kidney								X																	
Fibrous histiocytoma, metastatic, mesentery			X																						
Hepatoblastoma, metastatic, liver																			X						
Hepatocellular carcinoma, metastatic, liver				X												X									
Hepatocholangiocarcinoma, metastatic, liver			X																						
Histiocytic sarcoma									X			X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X					X			X
Carcinoma						X																			
Bilateral, adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Renal tubule, adenoma																									
Renal tubule, carcinoma, multiple								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X			X													
Lymphoma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg

Number of Days on Study	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	
Carcass ID Number	191	193	199	151	159	160	162	169	170	182	184	187	194	195	197	198	154	158	166	167	177	189	190	192	200	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X		X			X							X							7
Alveolar/bronchiolar adenoma, multiple											X										X					2
Alveolar/bronchiolar carcinoma					X															X			X			3
Alveolar/bronchiolar carcinoma, multiple													X													1
Carcinoma, metastatic, kidney																										1
Fibrous histiocytoma, metastatic, mesentery																										1
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X	X																			5
Carcinoma																										1
Bilateral, adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma																	X									1
Renal tubule, carcinoma, multiple																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant												X														1

Table A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	3/50 (6%)	3/50 (6%)	6/50 (12%)	5/50 (10%)
Adjusted rate[b]	6.4%	6.4%	13.8%	10.8%
Terminal rate[c]	3/37 (8%)	3/43 (7%)	4/34 (12%)	4/40 (10%)
First incidence (days)	726 (T)	726 (T)	676	618
Poly-3 test[d]	P=0.285	P=0.659	P=0.204	P=0.347
Harderian Gland: Adenoma				
Overall rate	7/50 (14%)	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted rate	14.6%	4.3%	4.6%	13.0%
Terminal rate	6/37 (16%)	2/43 (5%)	2/34 (6%)	6/40 (15%)
First incidence (days)	511	726 (T)	726 (T)	726 (T)
Poly-3 test	P=0.369	P=0.084N	P=0.105N	P=0.530N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	3/50 (6%)	2/50 (4%)	7/50 (14%)
Adjusted rate	14.6%	6.4%	4.6%	15.1%
Terminal rate	6/37 (16%)	3/43 (7%)	2/34 (6%)	6/40 (15%)
First incidence (days)	511	726 (T)	726 (T)	628
Poly-3 test	P=0.289	P=0.166N	P=0.105N	P=0.589
Intestine (Small): Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.4%	2.1%	0.0%	2.2%
Terminal rate	3/37 (8%)	1/43 (2%)	0/34 (0%)	1/40 (3%)
First incidence (days)	726 (T)	726 (T)	—[e]	726 (T)
Poly-3 test	P=0.352N	P=0.308N	P=0.135N	P=0.314N
Intestine (Small): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	6.4%	2.1%	0.0%	4.3%
Terminal rate	3/37 (8%)	1/43 (2%)	0/34 (0%)	1/40 (3%)
First incidence (days)	726 (T)	726 (T)	—	399
Poly-3 test	P=0.629N	P=0.308N	P=0.135N	P=0.503N
Liver: Hemangiosarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	6/50 (12%)	1/50 (2%)
Adjusted rate	2.1%	0.0%	13.5%	2.2%
Terminal rate	1/37 (3%)	0/43 (0%)	3/34 (9%)	1/40 (3%)
First incidence (days)	726 (T)	—	517	726 (T)
Poly-3 test	P=0.587	P=0.501N	P=0.047	P=0.755
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	18/50 (36%)	23/50 (46%)	20/50 (40%)
Adjusted rate	40.0%	38.4%	52.4%	42.8%
Terminal rate	17/37 (46%)	18/43 (42%)	20/34 (59%)	18/40 (45%)
First incidence (days)	688	726 (T)	659	618
Poly-3 test	P=0.425	P=0.519N	P=0.162	P=0.476
Liver: Hepatocellular Carcinoma				
Overall rate	17/50 (34%)	14/50 (28%)	14/50 (28%)	11/50 (22%)
Adjusted rate	34.4%	29.1%	29.6%	23.6%
Terminal rate	8/37 (22%)	11/43 (26%)	5/34 (15%)	9/40 (23%)
First incidence (days)	511	554	439	572
Poly-3 test	P=0.177N	P=0.365N	P=0.390N	P=0.172N

Table A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	33/50 (66%)	27/50 (54%)	33/50 (66%)	25/50 (50%)
Adjusted rate	66.6%	56.1%	69.2%	52.7%
Terminal rate	23/37 (62%)	24/43 (56%)	22/34 (65%)	21/40 (53%)
First incidence (days)	511	554	439	572
Poly-3 test	P=0.148N	P=0.195N	P=0.475	P=0.116N
Liver: Hepatoblastoma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.1%	2.1%	4.6%	6.5%
Terminal rate	1/37 (3%)	1/43 (2%)	2/34 (6%)	2/40 (5%)
First incidence (days)	726 (T)	726 (T)	726 (T)	618
Poly-3 test	P=0.181	P=0.759	P=0.470	P=0.299
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	18/50 (36%)	15/50 (30%)	15/50 (30%)	13/50 (26%)
Adjusted rate	36.4%	31.1%	31.8%	27.6%
Terminal rate	9/37 (24%)	12/43 (28%)	6/34 (18%)	10/40 (25%)
First incidence (days)	511	554	439	572
Poly-3 test	P=0.253N	P=0.369N	P=0.395N	P=0.240N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	33/50 (66%)	27/50 (54%)	34/50 (68%)	26/50 (52%)
Adjusted rate	66.6%	56.1%	71.3%	54.8%
Terminal rate	23/37 (62%)	24/43 (56%)	23/34 (68%)	22/40 (55%)
First incidence (days)	511	554	439	572
Poly-3 test	P=0.208N	P=0.195N	P=0.386	P=0.162N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	7/50 (14%)	12/50 (24%)	9/50 (18%)
Adjusted rate	12.7%	14.9%	26.8%	19.6%
Terminal rate	6/37 (16%)	7/43 (16%)	7/34 (21%)	9/40 (23%)
First incidence (days)	726 (T)	726 (T)	487	726 (T)
Poly-3 test	P=0.272	P=0.495	P=0.074	P=0.269
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	7/50 (14%)	6/50 (12%)	8/50 (16%)	4/50 (8%)
Adjusted rate	14.6%	12.8%	17.8%	8.7%
Terminal rate	5/37 (14%)	6/43 (14%)	5/34 (15%)	4/40 (10%)
First incidence (days)	511	726 (T)	503	726 (T)
Poly-3 test	P=0.246N	P=0.519N	P=0.444	P=0.287N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	12/50 (24%)	13/50 (26%)	19/50 (38%)	13/50 (26%)
Adjusted rate	25.0%	27.7%	40.9%	28.2%
Terminal rate	10/37 (27%)	13/43 (30%)	11/34 (32%)	13/40 (33%)
First incidence (days)	511	726 (T)	487	726 (T)
Poly-3 test	P=0.481	P=0.471	P=0.074	P=0.450
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	9/50 (18%)	2/50 (4%)
Adjusted rate	6.3%	4.3%	20.1%	4.3%
Terminal rate	1/37 (3%)	2/43 (5%)	5/34 (15%)	1/40 (3%)
First incidence (days)	624	726 (T)	517	618
Poly-3 test	P=0.442N	P=0.508N	P=0.046	P=0.513N

Table A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	9/50 (18%)	4/50 (8%)
Adjusted rate	8.4%	6.4%	20.1%	8.6%
Terminal rate	2/37 (5%)	3/43 (7%)	5/34 (15%)	3/40 (8%)
First incidence (days)	624	726 (T)	517	618
Poly-3 test	P=0.550	P=0.509N	P=0.092	P=0.628
All Organs: Benign Neoplasms				
Overall rate	30/50 (60%)	25/50 (50%)	32/50 (64%)	32/50 (64%)
Adjusted rate	62.3%	53.3%	70.4%	66.2%
Terminal rate	27/37 (73%)	25/43 (58%)	23/34 (68%)	27/40 (68%)
First incidence (days)	511	726 (T)	487	399
Poly-3 test	P=0.241	P=0.245N	P=0.269	P=0.426
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	24/50 (48%)	27/50 (54%)	21/50 (42%)
Adjusted rate	56.0%	49.8%	55.3%	43.5%
Terminal rate	16/37 (43%)	20/43 (47%)	14/34 (41%)	14/40 (35%)
First incidence (days)	511	554	439	566
Poly-3 test	P=0.150N	P=0.339N	P=0.552N	P=0.149N
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	35/50 (70%)	43/50 (86%)	41/50 (82%)
Adjusted rate	90.0%	72.6%	87.4%	82.5%
Terminal rate	33/37 (89%)	31/43 (72%)	28/34 (82%)	32/40 (80%)
First incidence (days)	511	554	439	399
Poly-3 test	P=0.518N	P=0.022N	P=0.460N	P=0.212N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

Table A4a
Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hepatoblastoma
Historical Incidence in Controls Given NTP-2000 Diet			
Acrylonitrile (gavage)	0/50	2/50	0/50
trans-Cinnamaldehyde (feed)	0/100	0/100	0/100
Citral (feed)	0/100	2/100	0/100
Decalin (inhalation)	0/50	1/50	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	2/50	0/50
Dipropylene glycol (drinking water)	1/50	0/50	0/50
Elmiron® (gavage)	0/50	2/50	1/50
2,4-Hexadienal (gavage)	0/50	1/50	2/50
Indium phosphide (inhalation)	0/50	2/50	0/50
60-Hz Magnetic fields (whole body exposure)	0/100	4/100	2/100
Methacrylonitrile (gavage)	0/49	1/49	1/49
2-Methylimidazole (feed)	0/50	1/50	0/50
o-Nitrotoluene (feed)	0/60	1/60	1/60
p-Nitrotoluene (feed)	0/50	1/50	0/50
Propylene glycol mono-*t*-butyl ether (inhalation)	0/50	2/50	0/50
Riddelliine (gavage)	0/50	2/50	3/50
Sodium nitrite (drinking water)	0/50	2/50	5/50
Stoddard solvent (Type IIC) (inhalation)	1/50	0/50	0/50
Triethanolamine (dermal)	0/50	1/50	1/50
Vanadium pentoxide (inhalation)	0/50	1/50	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	2/1,159 (0.2%)	28/1,159 (2.4%)	16/1,159 (1.4%)
Mean ± standard deviation	0.2% ± 0.6%	2.5% ± 1.4%	1.5% ± 2.6%
Range	0%-2%	0%-4%	0%-10%

[a] Data as of March 3, 2003

Table A4b
Historical Incidence of Hemangioma or Hemangiosarcoma (All Organs) in Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence in Controls Given NTP-2000 Diet			
Acrylonitrile (gavage)	2/50	3/50	5/50
trans-Cinnamaldehyde (feed)	3/100	2/100	5/100
Citral (feed)	2/100	3/100	5/100
Decalin (inhalation)	0/50	1/50	1/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	3/50	3/50
Dipropylene glycol (drinking water)	2/50	0/50	2/50
Elmiron® (gavage)	0/50	6/50	6/50
2,4-Hexadienal (gavage)	1/50	4/50	5/50
Indium phosphide (inhalation)	0/50	3/50	3/50
60-Hz Magnetic fields (whole body exposure)	0/100	6/100	6/100
Methacrylonitrile (gavage)	0/49	3/49	3/49
2-Methylimidazole (feed)	0/50	2/50	2/50
o-Nitrotoluene (feed)	1/60	4/60	5/60
p-Nitrotoluene (feed)	0/50	1/50	1/50
Propylene glycol mono-*t*-butyl ether (inhalation)	1/50	3/50	4/50
Riddelliine (gavage)	0/50	3/50	3/50
Sodium nitrite (drinking water)	0/50	7/50	7/50
Stoddard solvent (Type IIC) (inhalation)	1/50	1/50	2/50
Triethanolamine (dermal)	1/50	3/50	4/50
Vanadium pentoxide (inhalation)	0/50	1/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	14/1,159 (1.2%)	59/1,159 (5.1%)	73/1,159 (6.3%)
Mean ± standard deviation	1.1% ± 1.4%	5.3% ± 3.4%	6.4% ± 3.3%
Range	0%-4%	0%-14%	2%-14%

[a] Data as of March 3, 2003

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine[a]

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	5	2	6	8
Natural deaths	8	5	10	2
Survivors				
Terminal sacrifice	37	43	34	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(48)	(49)	(50)	(47)
Necrosis	1 (2%)			
Intestine large, colon	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	
Goblet cell, hyperplasia			1 (2%)	
Intestine large, cecum	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Epithelium, hyperplasia	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Diverticulum	1 (2%)			
Epithelium, hyperplasia		1 (2%)		
Peyer's patch, hyperplasia, lymphoid	1 (2%)			1 (2%)
Serosa, inflammation, granulomatous		1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(50)
Muscularis, infiltration cellular, mononuclear cell			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	2 (4%)	6 (12%)	3 (6%)	2 (4%)
Clear cell focus	19 (38%)	23 (46%)	14 (28%)	11 (22%)
Eosinophilic focus	9 (18%)	20 (40%)	31 (62%)	30 (60%)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	1 (2%)		1 (2%)	
Infiltration cellular, lymphoid	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, acute	1 (2%)			
Inflammation, chronic	9 (18%)	14 (28%)	10 (20%)	11 (22%)
Mixed cell focus	13 (26%)	11 (22%)	15 (30%)	8 (16%)
Necrosis, focal	4 (8%)	3 (6%)	7 (14%)	6 (12%)
Vacuolization cytoplasmic, focal	2 (4%)	1 (2%)	3 (6%)	5 (10%)
Centrilobular, necrosis		1 (2%)	1 (2%)	
Mesentery	(3)	(3)	(5)	(7)
Inflammation, granulomatous			1 (20%)	
Artery, inflammation, chronic				1 (14%)
Fat, necrosis	3 (100%)	3 (100%)	4 (80%)	5 (71%)
Oral mucosa	(31)	(26)	(35)	(30)
Inflammation, chronic	31 (100%)	26 (100%)	35 (100%)	30 (100%)
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy		1 (2%)		
Duct, cyst				1 (2%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
Ulcer			1 (2%)	1 (2%)
Epithelium, cyst				1 (2%)
Epithelium, hyperplasia, focal	3 (6%)		3 (6%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid				1 (2%)
Ulcer			2 (4%)	
Epithelium, hyperplasia, focal				1 (2%)
Glands, ectasia		1 (2%)		
Tooth	(19)	(18)	(14)	(13)
Malformation	19 (100%)	18 (100%)	14 (100%)	13 (100%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic				1 (2%)
Aorta, mineralization		1 (2%)		
Pulmonary vein, thrombosis				1 (2%)
Heart	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	3 (6%)	1 (2%)		
Inflammation, acute	1 (2%)			
Inflammation, chronic				2 (4%)
Artery, inflammation, chronic		1 (2%)		3 (6%)
Atrium, thrombosis	1 (2%)	1 (2%)		
Coronary artery, inflammation, chronic				1 (2%)
Myocardium, degeneration		1 (2%)		
Myocardium, mineralization	1 (2%)		1 (2%)	2 (4%)
Valve, inflammation, chronic		1 (2%)		
Ventricle, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia, focal	8 (16%)	4 (8%)	3 (6%)	1 (2%)
Hypertrophy, focal	16 (32%)	21 (42%)	10 (20%)	10 (20%)
Necrosis			1 (2%)	
Subcapsular, hyperplasia	39 (78%)	45 (90%)	40 (80%)	40 (80%)
Zona glomerulosa, hyperplasia		2 (4%)	3 (6%)	1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia, focal				2 (4%)
Necrosis			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	45 (90%)	43 (86%)	43 (86%)	32 (64%)
Pituitary gland	(50)	(49)	(49)	(50)
Pars distalis, hyperplasia	1 (2%)	2 (4%)		1 (2%)
Pars intermedia, hyperplasia	1 (2%)			3 (6%)
Thyroid gland	(50)	(50)	(49)	(50)
Follicle, cyst	1 (2%)	1 (2%)		1 (2%)
General Body System				
None				

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Genital System				
Coagulating gland			(1)	(1)
Cyst			1 (100%)	
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic		1 (2%)		
Preputial gland	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Cyst	10 (20%)	14 (28%)	11 (22%)	15 (30%)
Inflammation, chronic	1 (2%)			2 (4%)
Inflammation, suppurative		1 (2%)		3 (6%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)	
Testes	(50)	(50)	(50)	(50)
Inflammation, granulomatous				1 (2%)
Germinal epithelium, atrophy	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Germinal epithelium, mineralization		2 (4%)	1 (2%)	
Hematopoietic System				
Lymph node, mesenteric	(50)	(48)	(48)	(50)
Congestion			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Spleen	(49)	(50)	(50)	(50)
Atrophy	4 (8%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	14 (29%)	20 (40%)	17 (34%)	19 (38%)
Lymphoid follicle, hematopoietic cell proliferation	1 (2%)		1 (2%)	
Red pulp, infiltration cellular, mononuclear cell	1 (2%)			
Thymus	(48)	(47)	(48)	(48)
Atrophy	38 (79%)	37 (79%)	37 (77%)	38 (79%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Dermis, edema			1 (2%)	
Epidermis, hyperkeratosis	1 (2%)			
Epidermis, ulcer	1 (2%)			
Site of application, epidermis, hyperkeratosis	3 (6%)			
Site of application, epidermis, hyperplasia	5 (10%)	44 (88%)	45 (90%)	49 (98%)
Site of application, epidermis, inflammation, suppurative	1 (2%)	11 (22%)	33 (66%)	42 (84%)
Site of application, epidermis, ulcer		3 (6%)	20 (40%)	47 (94%)
Subcutaneous tissue, site of application, dermis, inflammation, chronic	1 (2%)	15 (30%)	40 (80%)	49 (98%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	200 mg/kg	630 mg/kg	2,000 mg/kg
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression				1 (2%)
Spinal cord	(1)			
Necrosis	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic	1 (2%)			
Inflammation, granulomatous	2 (4%)			
Alveolar epithelium, hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Bronchus, hyperplasia, focal		1 (2%)		
Perivascular, infiltration cellular, lymphoid				1 (2%)
Vein, thrombosis				1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)		1 (2%)	
Polyp, inflammatory		1 (2%)		
Respiratory epithelium, mineralization				1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Degeneration	1 (2%)			
Cornea, inflammation, acute				1 (2%)
Retrobulbar, inflammation, suppurative	1 (2%)			
Harderian gland	(50)	(50)	(49)	(50)
Hyperplasia	3 (6%)	5 (10%)	6 (12%)	7 (14%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis		1 (2%)		
Infarct	2 (4%)	3 (6%)	2 (4%)	4 (8%)
Inflammation, acute	2 (4%)			
Metaplasia, osseous	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Nephropathy	39 (78%)	42 (84%)	37 (74%)	40 (80%)
Artery, thrombosis		1 (2%)		
Capsule, inflammation, chronic			1 (2%)	
Glomerulus, cyst		2 (4%)		2 (4%)
Papilla, necrosis			1 (2%)	
Renal tubule, cyst	4 (8%)	2 (4%)		4 (8%)
Renal tubule, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Urinary bladder	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Inflammation, acute	1 (2%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DERMAL STUDY OF TRIETHANOLAMINE

TABLE B1 Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine 88
TABLE B2 Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine 92
TABLE B3 Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine 116
TABLE B4 Historical Incidence of Liver Neoplasms in Control Female $B6C3F_1$ Mice 119
TABLE B5 Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine 120

Table B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine[a]

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	8	10	5	10
Natural deaths	7	6	4	7
Survivors				
Died last week of study	1			
Terminal sacrifice	34	34	41	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Leiomyoma				1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus				1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Polyp adenomatous			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	5 (10%)	8 (16%)	4 (8%)	5 (10%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	9 (18%)	15 (30%)	13 (26%)	16 (32%)
Hepatocellular adenoma, multiple		3 (6%)	7 (14%)	17 (34%)
Histiocytic sarcoma	4 (8%)	5 (10%)		3 (6%)
Mesentery	(11)	(6)	(4)	(9)
Liposarcoma			1 (25%)	
Oral mucosa	(26)	(26)	(31)	(31)
Histiocytic sarcoma	1 (4%)			
Pancreas	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)		2 (4%)	4 (8%)
Squamous cell papilloma, multiple			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)

Table B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Subcapsular, adenoma				1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign	1 (2%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	8 (16%)	5 (10%)	5 (10%)	5 (10%)
Pars distalis, carcinoma				1 (2%)
Pars intermedia, adenoma		3 (6%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicle, adenoma			1 (2%)	3 (6%)
Follicle, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Ovary	(50)	(50)	(50)	(50)
Cystadenoma	1 (2%)	1 (2%)		1 (2%)
Granulosa cell tumor malignant				1 (2%)
Histiocytic sarcoma	2 (4%)	2 (4%)		1 (2%)
Luteoma	1 (2%)	1 (2%)		
Teratoma benign				1 (2%)
Tubulostromal adenoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)	3 (6%)		1 (2%)
Leiomyosarcoma		1 (2%)		2 (4%)
Polyp stromal	1 (2%)		3 (6%)	1 (2%)
Vagina				(1)
Leiomyosarcoma, metastatic, uterus				1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Lymph node	(6)	(7)	(4)	(6)
Iliac, histiocytic sarcoma		1 (14%)		
Lumbar, histiocytic sarcoma	1 (17%)			
Mediastinal, liposarcoma, metastatic, mesentery			1 (25%)	
Renal, histiocytic sarcoma		1 (14%)		
Lymph node, mandibular	(49)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(48)	(48)
Histiocytic sarcoma		3 (6%)		
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	1 (2%)
Histiocytic sarcoma	2 (4%)	3 (6%)		
Thymus	(49)	(49)	(49)	(49)
Histiocytic sarcoma		1 (2%)		

Table B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Sebaceous gland, adenoma	1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, hemangiosarcoma, multiple	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, melanoma malignant multiple	1 (2%)			
Subcutaneous tissue, osteosarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)		
Skeletal muscle	(1)	(2)	(1)	(3)
Hemangiosarcoma, metastatic, spleen			1 (100%)	
Rhabdomyosarcoma	1 (100%)	2 (100%)		2 (67%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hemangiosarcoma, metastatic, heart	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)		2 (4%)
Histiocytic sarcoma	4 (8%)	4 (8%)		1 (2%)
Liposarcoma, metastatic, mesentery			1 (2%)	
Osteosarcoma, metastatic, bone		1 (2%)		
Osteosarcoma, metastatic, skin	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(49)	(50)	(50)	(50)
Harderian gland	(49)	(50)	(50)	(50)
Adenoma	5 (10%)	5 (10%)	3 (6%)	3 (6%)
Carcinoma	2 (4%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	3 (6%)		
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(50)	(49)	(49)

Table B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	4 (8%)	5 (10%)		3 (6%)
Lymphoma malignant	8 (16%)	9 (18%)	6 (12%)	8 (16%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	38	41	35	44
Total primary neoplasms	63	67	58	84
Total animals with benign neoplasms	24	28	27	38
Total benign neoplasms	33	35	41	57
Total animals with malignant neoplasms	27	26	16	21
Total malignant neoplasms	30	32	17	27
Total animals with metastatic neoplasms	6	4	2	3
Total metastatic neoplasms	6	4	3	4

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	329	469	532	595	617	617	619	619	640	652	653	657	666	711	717	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	230	214	206	242	223	237	209	233	231	204	227	211	210	238	222	203	207	218	220	243	244	201	212	212	216
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma				X						X										X					X
Hepatocellular carcinoma, multiple															X										
Hepatocellular adenoma						X				X			X							X					
Histiocytic sarcoma					X	X			X			X													
Mesentery	+										+						+			+					+
Oral mucosa			+	+								+				+		+	+			+		+	
Histiocytic sarcoma												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Histiocytic sarcoma												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X			X												X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, carcinoma																									
General Body System																									
None																									

+: Tissue examined microscopically — M: Missing tissue — X: Lesion present
A: Autolysis precludes examination — I: Insufficient tissue — Blank: Not examined

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 2 1	2 2 5	2 2 9	2 3 2	2 3 4	2 3 9	2 4 1	2 4 5	2 4 8	2 5 0	2 0 5	2 0 8	2 1 3	2 1 5	2 1 7	2 1 9	2 2 4	2 2 6	2 2 8	2 3 5	2 3 6	2 4 0	2 4 6	2 4 7	2 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																				X						1
Hepatocellular carcinoma																								X		5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X																X			X	X			X		9
Histiocytic sarcoma																										4
Mesentery								+			+	+					+		+					+		11
Oral mucosa	+	+		+	+	+		+		+	+	+	+		+	+	+		+	+			+	+	+	26
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma							X																			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+	M	+	+	M	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X	X		X					X									8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, carcinoma																				X						1
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	329	469	532	595	617	617	619	619	640	652	653	657	666	711	717	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	230	214	206	242	223	237	209	233	231	204	227	211	210	238	222	203	207	218	220	243	244	201	202	212	216
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																	X								
Histiocytic sarcoma					X							X													
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X			X			X													
Polyp stromal																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymph node									+							+									
Lumbar, histiocytic sarcoma									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma					X				X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibrosarcoma													X												
Subcutaneous tissue, hemangiosarcoma, multiple																									
Subcutaneous tissue, histiocytic sarcoma					X																				
Subcutaneous tissue, melanoma malignant, multiple																									X
Subcutaneous tissue, osteosarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																						+			
Rhabdomyosarcoma																						X			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	221	225	229	232	234	239	241	245	248	250	205	208	213	215	217	219	224	226	228	235	236	240	246	247	249	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Histiocytic sarcoma																										2
Luteoma											X															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+							+			+														+	6
Lumbar, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma																					X					1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma, multiple																					X					1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, melanoma malignant, multiple																										1
Subcutaneous tissue, osteosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	329	469	532	595	617	617	619	619	640	652	653	657	666	711	717	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	230	214	206	242	223	237	209	233	231	204	227	211	210	238	222	203	207	218	220	243	244	201	202	212	216
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									X
Carcinoma, metastatic, harderian gland			X																						
Hemangiosarcoma, metastatic, heart								X																	
Hepatocellular carcinoma, metastatic, liver															X					X					X
Histiocytic sarcoma					X	X			X			X													
Osteosarcoma, metastatic, skin										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma			X				X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X						X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X	X			X			X													
Lymphoma malignant																X		X					X		

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	221	225	229	232	234	239	241	245	248	250	205	208	213	215	217	219	224	226	228	235	236	240	246	247	249	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X						X															X			3
Alveolar/bronchiolar carcinoma																			X							2
Carcinoma, metastatic, harderian gland																										1
Hemangiosarcoma, metastatic, heart																										1
Hepatocellular carcinoma, metastatic, liver																										3
Histiocytic sarcoma																										4
Osteosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X	X							X					X												5
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										4
Lymphoma malignant			X								X		X		X										X	8

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	221	239	444	510	594	601	610	665	665	665	674	674	674	686	698	708	729	729	729	729	729	729	729	730	730
Carcass ID Number	297	265	282	256	274	286	259	267	273	275	287	292	296	271	300	288	253	254	264	266	269	270	272	252	255
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Hepatocellular carcinoma						X	X					X				X	X								
Hepatocellular adenoma								X							X		X	X	X	X					X
Hepatocellular adenoma, multiple																						X			
Histiocytic sarcoma			X	X							X														
Mesentery							+									+	+					+			
Oral mucosa					+				+			+				+	+		+	+	+	+		+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X	X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Histiocytic sarcoma				X																					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 7	2 6 0	2 6 1	2 7 8	2 8 0	2 8 4	2 8 9	2 9 0	2 9 3	2 9 4	2 5 1	2 5 8	2 6 2	2 6 3	2 6 8	2 7 6	2 7 7	2 7 9	2 8 1	2 8 3	2 8 5	2 9 1	2 9 5	2 9 8	2 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma															X	X							X			8
Hepatocellular adenoma					X					X			X		X			X		X	X		X			15
Hepatocellular adenoma, multiple																	X							X		3
Histiocytic sarcoma									X						X											5
Mesentery																	+	+								6
Oral mucosa	+			+	+			+	+	+	+	+	+			+	+				+	+	+		+	26
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																			X							1
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X										X								X		5
Pars intermedia, adenoma									X											X						3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	221	239	444	510	594	601	610	665	665	665	674	674	674	686	698	708	729	729	729	729	729	729	729	730	730
Carcass ID Number	297	265	282	256	274	286	259	267	273	275	287	292	296	271	300	288	253	254	264	266	269	270	272	252	255
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X				
Histiocytic sarcoma			X	X																					
Luteoma																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X	X							X														
Leiomyosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node							+	+		+	+			+				+	M						
Iliac, histiocytic sarcoma											X														
Renal, histiocytic sarcoma											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X							X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X							X														
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma													X												
Skeletal muscle					+																	+			
Rhabdomyosarcoma					X																	X			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver												X													
Histiocytic sarcoma			X	X							X														
Osteosarcoma, metastatic, bone													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	257	260	261	278	280	284	289	290	293	294	251	258	262	263	268	276	277	279	281	283	285	291	295	298	299	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Histiocytic sarcoma																										2
Luteoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Leiomyosarcoma																			X							1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node							+																			7
Iliac, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma									X																	3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Rhabdomyosarcoma																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Alveolar/bronchiolar carcinoma												X	X													2
Hepatocellular carcinoma, metastatic, liver															X	X										3
Histiocytic sarcoma									X																	4
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	221	239	444	510	594	601	610	665	665	665	674	674	674	686	698	708	729	729	729	729	729	729	729	730	730
Carcass ID Number	297	265	282	256	274	286	259	267	273	275	287	292	296	271	300	288	253	254	264	266	269	270	272	252	255
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X				X									X						X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X	X							X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X	X							X														
Lymphoma malignant							X			X				X				X	X						X

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	257	260	261	278	280	284	289	290	293	294	251	258	262	263	268	276	277	279	281	283	285	291	295	298	299	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X						X											5
Lymphoma malignant			X					X								X										9

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	0	3	4	4	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	3	4	4	7	8	8	7	9	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3
	2	8	4	7	3	1	6	4	2	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	4	1	2	2	1	4	0	3	0	0	0	0	3	4	4	0	0	0	1	1	1	1	2	2
	5	9	1	6	7	2	3	7	7	1	3	4	8	4	4	7	2	6	9	4	5	7	9	0	5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X																		
Hepatocellular adenoma			X			X					X				X					X	X			X	
Hepatocellular adenoma, multiple												X	X					X							
Mesentery					+																				
Liposarcoma					X																				
Oral mucosa								+		+	+	+	+	+	+	+		+	+	+	+		+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X										X					
Squamous cell papilloma, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X					X				
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma									X																
General Body System																									
None																									

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	328	329	330	331	332	338	342	346	310	313	316	318	321	322	323	324	333	335	336	339	340	341	345	348	350	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous			X																							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X												X						X			4
Hepatocellular adenoma	X		X					X			X			X											X	13
Hepatocellular adenoma, multiple										X			X			X						X				7
Mesentery										+		+	+													4
Liposarcoma																										1
Oral mucosa		+	+	+	+	+			+	+			+			+	+		+		+	+	+	+	+	31
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Squamous cell papilloma, multiple								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																							+			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X							X	X																	5
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenoma																										1
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	062	338	444	447	573	581	586	674	692	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730
Carcass ID Number	305	349	311	326	327	312	343	307	337	301	303	304	308	334	344	347	302	306	309	314	315	317	319	320	325
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+																	
Mediastinal, liposarcoma, metastatic, mesentery					X																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																				X		X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+	
Hemangiosarcoma, metastatic, spleen																								X	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																							
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X										X		
Alveolar/bronchiolar carcinoma																							X		
Liposarcoma, metastatic, mesentery					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	328	329	330	331	332	338	342	346	310	313	316	318	321	322	323	324	333	335	336	339	340	341	345	348	350	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X							X																	X	3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+										+							4
Mediastinal, liposarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangiosarcoma, metastatic, spleen																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma												X				X										3
Liposarcoma, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X						X										3

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	062	338	444	447	573	581	586	674	692	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730
Carcass ID Number	305	349	311	326	327	312	343	307	337	301	303	304	308	334	344	347	302	306	309	314	315	317	319	320	325
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X	X	X									X							

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	328	329	330	331	332	338	342	346	310	313	316	318	321	322	323	324	333	335	336	339	340	341	345	348	350	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant															X				X							6

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	0 7 0	4 1 0	5 2 7	5 6 7	5 9 5	6 0 4	6 1 7	6 1 9	6 5 3	6 8 5	6 8 5	7 0 1	7 0 1	7 0 9	7 1 2	7 1 7	7 2 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 6 5	3 7 7	3 5 4	3 5 3	3 9 1	3 6 8	3 5 2	3 8 0	3 5 7	3 7 8	3 8 5	3 8 3	3 8 7	3 8 8	3 9 8	3 6 4	3 7 0	3 9 0	3 5 6	3 6 7	3 7 6	3 9 3	3 5 1	3 5 8	3 6 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus																		X							
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X											X		
Hepatocellular adenoma						X				X	X	X			X	X			X				X	X	
Hepatocellular adenoma, multiple									X									X		X	X	X			X
Histiocytic sarcoma							X	X																	
Mesentery							+												+						
Oral mucosa				+		+			+					+	+		+		+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									X	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																				X		X			
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma									X						X										
General Body System																									
None																									

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	361	363	366	369	372	373	375	379	384	389	392	394	399	355	359	362	371	374	381	382	386	395	396	397	400	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																		X								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma				X									X											X		5
Hepatocellular adenoma			X	X			X				X			X							X			X		16
Hepatocellular adenoma, multiple	X	X			X	X		X	X	X					X		X			X		X				17
Histiocytic sarcoma															X											3
Mesentery					+			+	+						+						+	+		+		9
Oral mucosa	+		+	+		+			+	+		+		+	+	+	+	+	+	+	+	+		+	+	31
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X					X					4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma														X												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X		X							X								5
Pars distalis, carcinoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenoma							X																			3
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	070	410	527	567	595	604	617	619	653	685	685	701	701	709	712	717	726	726	729	729	729	729	730	730	730
Carcass ID Number	365	377	354	353	391	368	352	380	357	378	385	383	387	388	398	364	370	390	356	367	376	393	351	358	360
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma						X																			
Granulosa cell tumor malignant					X																				
Histiocytic sarcoma							X																		
Teratoma benign	X																								
Tubulostromal adenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Leiomyosarcoma					X													X							
Polyp stromal								X																	
Vagina																		+							
Leiomyosarcoma, metastatic, uterus																		X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node				+																+		+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, hemangiosarcoma																X									
Subcutaneous tissue, histiocytic sarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											+
Rhabdomyosarcoma																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver												X											X		
Histiocytic sarcoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	361	363	366	369	372	373	375	379	384	389	392	394	399	355	359	362	371	374	381	382	386	395	396	397	400	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Granulosa cell tumor malignant																										1
Histiocytic sarcoma																										1
Teratoma benign																										1
Tubulostromal adenoma														X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leiomyosarcoma																										2
Polyp stromal																										1
Vagina																										1
Leiomyosarcoma, metastatic, uterus																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node											+											+		+		6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle									+																	3
Rhabdomyosarcoma									X																	2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Alveolar/bronchiolar carcinoma					X																					1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	070	410	527	567	595	604	617	619	653	685	685	701	701	709	712	717	726	726	729	729	729	729	730	730	730
Carcass ID Number	365	377	354	353	391	368	352	380	357	378	385	383	387	388	398	364	370	390	356	367	376	393	351	358	360
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X	X																	
Lymphoma malignant				X										X						X			X		

Table B2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	361	363	366	369	372	373	375	379	384	389	392	394	399	355	359	362	371	374	381	382	386	395	396	397	400	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X	X											3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											3
Lymphoma malignant	X		X																				X	X		8

Table B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	5/50 (10%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate[b]	11.3%	11.3%	6.7%	6.7%
Terminal rate[c]	4/35 (11%)	3/34 (9%)	3/41 (7%)	2/32 (6%)
First incidence (days)	666	594	729 (T)	527
Poly-3 test[d]	P=0.279N	P=0.628	P=0.353N	P=0.350N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate	15.4%	11.3%	6.7%	6.7%
Terminal rate	4/35 (11%)	3/34 (9%)	3/41 (7%)	2/32 (6%)
First incidence (days)	532	594	729 (T)	527
Poly-3 test	P=0.161N	P=0.397N	P=0.164N	P=0.162N
Liver: Hepatocellular Adenoma				
Overall rate	9/50 (18%)	18/50 (36%)	20/50 (40%)	33/50 (66%)
Adjusted rate	19.9%	41.0%	43.5%	72.4%
Terminal rate	6/35 (17%)	16/34 (47%)	18/41 (44%)	25/32 (78%)
First incidence (days)	617	665	444	604
Poly-3 test	P<0.001	P=0.024	P=0.012	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	8/50 (16%)	4/50 (8%)	5/50 (10%)
Adjusted rate	13.3%	17.9%	8.9%	11.3%
Terminal rate	3/35 (9%)	4/34 (12%)	3/41 (7%)	4/32 (13%)
First incidence (days)	595	601	586	701
Poly-3 test	P=0.354N	P=0.382	P=0.367N	P=0.509N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	12/50 (24%)	23/50 (46%)	24/50 (48%)	34/50 (68%)
Adjusted rate	26.3%	51.0%	51.7%	74.6%
Terminal rate	7/35 (20%)	17/34 (50%)	21/41 (51%)	26/32 (81%)
First incidence (days)	595	601	444	604
Poly-3 test	P<0.001	P=0.011	P=0.009	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	2.3%	4.5%	2.3%
Terminal rate	3/35 (9%)	1/34 (3%)	2/41 (5%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.344N	P=0.310N	P=0.495N	P=0.304N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.5%	4.6%	6.7%	2.3%
Terminal rate	2/35 (6%)	2/34 (6%)	3/41 (7%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.370N	P=0.689	P=0.505	P=0.499N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	11.3%	6.9%	9.0%	4.5%
Terminal rate	5/35 (14%)	3/34 (9%)	4/41 (10%)	2/32 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.224N	P=0.364N	P=0.493N	P=0.215N

Table B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/50 (16%)	5/50 (10%)	5/50 (10%)	5/50 (10%)
Adjusted rate	17.8%	11.5%	11.2%	11.3%
Terminal rate	6/35 (17%)	5/34 (15%)	5/41 (12%)	5/32 (16%)
First incidence (days)	619	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.344N	P=0.294N	P=0.277N	P=0.283N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	5/50 (10%)	5/50 (10%)	6/50 (12%)
Adjusted rate	17.8%	11.5%	11.2%	13.6%
Terminal rate	6/35 (17%)	5/34 (15%)	5/41 (12%)	6/32 (19%)
First incidence (days)	619	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.488N	P=0.294N	P=0.277N	P=0.396N
Pituitary Gland (Pars Intermedia): Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	6.9%	2.2%	0.0%
Terminal rate	0/35 (0%)	3/34 (9%)	1/41 (2%)	0/32 (0%)
First incidence (days)	—[e]	729 (T)	729 (T)	—
Poly-3 test	P=0.280N	P=0.116	P=0.502	—[f]
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.5%	0.0%	6.7%	9.0%
Terminal rate	2/35 (6%)	0/34 (0%)	3/41 (7%)	3/32 (9%)
First incidence (days)	729 (T)	—	729 (T)	712
Poly-3 test	P=0.113	P=0.240N	P=0.505	P=0.338
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.2%	6.7%
Terminal rate	0/35 (0%)	0/34 (0%)	0/41 (0%)	1/32 (3%)
First incidence (days)	—	—	692	653
Poly-3 test	P=0.023	—	P=0.503	P=0.120
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.3%	0.0%	2.2%	6.7%
Terminal rate	1/35 (3%)	0/34 (0%)	0/41 (0%)	1/32 (3%)
First incidence (days)	729 (T)	—	692	653
Poly-3 test	P=0.084	P=0.503N	P=0.757N	P=0.309
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.3%	0.0%	6.7%	2.2%
Terminal rate	1/35 (3%)	0/34 (0%)	3/41 (7%)	0/32 (0%)
First incidence (days)	729 (T)	—	729 (T)	619
Poly-3 test	P=0.602	P=0.503N	P=0.309	P=0.758N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.7%	2.3%	2.2%	4.5%
Terminal rate	2/35 (6%)	1/34 (3%)	1/41 (2%)	1/32 (3%)
First incidence (days)	619	729 (T)	729 (T)	717
Poly-3 test	P=0.613N	P=0.313N	P=0.304N	P=0.503N

Table B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	9.0%	2.3%	2.2%	4.5%
Terminal rate	3/35 (9%)	1/34 (3%)	1/41 (2%)	1/32 (3%)
First incidence (days)	619	729 (T)	729 (T)	717
Poly-3 test	P=0.477N	P=0.185N	P=0.178N	P=0.340N
All Organs: Histiocytic Sarcoma				
Overall rate	4/50 (8%)	5/50 (10%)	0/50 (0%)	3/50 (6%)
Adjusted rate	8.8%	11.1%	0.0%	6.7%
Terminal rate	0/35 (0%)	2/34 (6%)	0/41 (0%)	1/32 (3%)
First incidence (days)	617	444	—	617
Poly-3 test	P=0.396N	P=0.495	P=0.063N	P=0.506N
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	9/50 (18%)	6/50 (12%)	8/50 (16%)
Adjusted rate	18.1%	20.3%	13.2%	17.8%
Terminal rate	8/35 (23%)	6/34 (18%)	3/41 (7%)	6/32 (19%)
First incidence (days)	729 (T)	610	586	567
Poly-3 test	P=0.530N	P=0.504	P=0.363N	P=0.595N
All Organs: Benign Neoplasms				
Overall rate	24/50 (48%)	28/50 (56%)	27/50 (54%)	38/50 (76%)
Adjusted rate	52.7%	62.6%	58.5%	79.8%
Terminal rate	20/35 (57%)	23/34 (68%)	24/41 (59%)	27/32 (84%)
First incidence (days)	617	594	444	70
Poly-3 test	P=0.003	P=0.226	P=0.362	P=0.003
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	26/50 (52%)	16/50 (32%)	21/50 (42%)
Adjusted rate	56.2%	54.5%	34.7%	45.1%
Terminal rate	16/35 (46%)	14/34 (41%)	12/41 (29%)	12/32 (38%)
First incidence (days)	532	444	573	567
Poly-3 test	P=0.179N	P=0.514N	P=0.027N	P=0.188N
All Organs: Benign or Malignant				
Overall rate	38/50 (76%)	41/50 (82%)	35/50 (70%)	44/50 (88%)
Adjusted rate	79.2%	85.3%	74.0%	89.7%
Terminal rate	27/35 (77%)	27/34 (79%)	29/41 (71%)	29/32 (91%)
First incidence (days)	532	444	444	70
Poly-3 test	P=0.122	P=0.300	P=0.359N	P=0.119

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed

Table B4
Historical Incidence of Liver Neoplasms in Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet			
Acrylonitrile (gavage)	14/50	7/50	20/50
trans-Cinnamaldehyde (feed)	7/99	3/99	9/99
Citral (feed)	8/99	4/99	12/99
Decalin (inhalation)	7/49	4/49	11/49
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	3/50	6/50
Dipropylene glycol (drinking water)	11/50	7/50	17/50
Elmiron® (gavage)	7/50	3/50	10/50
2,4-Hexadienal (gavage)	11/50	3/50	13/50
Indium phosphide (inhalation)	12/50	6/50	18/50
60-Hz Magnetic fields (whole body exposure)	17/98	6/98	22/98
Methacrylonitrile (gavage)	9/50	2/50	10/50
2-Methylimidazole (feed)	3/50	2/50	4/50
o-Nitrotoluene (feed)	7/60	2/60	9/60
p-Nitrotoluene (feed)	6/49	3/49	8/49
Propylene glycol mono-*t*-butyl ether (inhalation)	14/49	4/49	18/49
Riddelliine (gavage)	9/49	8/49	16/49
Sodium nitrite (drinking water)	9/50	2/50	10/50
Stoddard solvent (Type IIC) (inhalation)	9/50	6/50	13/50
Triethanolamine (dermal	9/50	6/50	12/50
Vanadium pentoxide (inhalation)	6/50	6/50	12/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	179/1,152 (15.5%)	87/1,152 (7.6%)	250/1,152 (21.7%)
Mean ± standard deviation	16.3% ± 6.6%	8.1% ± 4.2%	22.8% ± 9.4%
Range	6%-29%	3%-14%	8%-40%

[a] Data as of March 3, 2003

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine[a]

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	8	10	5	10
Natural deaths	7	6	4	7
Survivors				
Died last week of study	1			
Terminal sacrifice	34	34	41	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(50)	(50)	(50)	(50)
Serosa, inflammation, chronic			1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Epithelium, necrosis	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Diverticulum				1 (2%)
Ulcer		1 (2%)		
Peyer's patch, hyperplasia	1 (2%)			
Peyer's patch, inflammation, suppurative			1 (2%)	
Serosa, inflammation, granulomatous				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal			1 (2%)	
Basophilic focus	4 (8%)		3 (6%)	3 (6%)
Clear cell focus	4 (8%)	3 (6%)	3 (6%)	5 (10%)
Eosinophilic focus	16 (32%)	22 (44%)	28 (56%)	32 (64%)
Fibrosis, focal	1 (2%)			
Hematopoietic cell proliferation	4 (8%)	3 (6%)	3 (6%)	4 (8%)
Hepatodiaphragmatic nodule		2 (4%)		
Infiltration cellular, lymphoid	26 (52%)	30 (60%)	36 (72%)	20 (40%)
Inflammation, chronic	14 (28%)	27 (54%)	22 (44%)	15 (30%)
Mixed cell focus	5 (10%)	8 (16%)	14 (28%)	11 (22%)
Necrosis, focal		5 (10%)	1 (2%)	3 (6%)
Vacuolization cytoplasmic, focal	8 (16%)	1 (2%)	6 (12%)	6 (12%)
Centrilobular, cytomegaly, diffuse			1 (2%)	
Centrilobular, necrosis	1 (2%)		1 (2%)	
Mesentery	(11)	(6)	(4)	(9)
Inflammation, chronic	1 (9%)			
Fat, necrosis	10 (91%)	6 (100%)	3 (75%)	9 (100%)
Lymphatic, angiectasis	1 (9%)			
Oral mucosa	(26)	(26)	(31)	(31)
Inflammation, chronic	26 (100%)	26 (100%)	31 (100%)	31 (100%)
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	1 (2%)	3 (6%)	1 (2%)	
Acinus, hyperplasia		1 (2%)		
Duct, cyst	1 (2%)	2 (4%)	1 (2%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, suppurative		1 (2%)		
Ulcer		1 (2%)	2 (4%)	
Epithelium, cyst				1 (2%)
Epithelium, hyperplasia, focal		1 (2%)		1 (2%)
Epithelium, mineralization			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, acute			1 (2%)	
Ulcer		1 (2%)		1 (2%)
Epithelium, cyst	1 (2%)		1 (2%)	
Epithelium, hyperplasia, focal	1 (2%)		1 (2%)	1 (2%)
Serosa, inflammation, chronic				1 (2%)
Tooth			(1)	
Inflammation, chronic			1 (100%)	
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic			2 (4%)	
Aorta, mineralization	1 (2%)	2 (4%)		
Heart	(50)	(50)	(50)	(50)
Artery, inflammation, chronic	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Atrium, thrombosis	2 (4%)			
Myocardium, degeneration	4 (8%)		1 (2%)	
Myocardium, inflammation, acute	1 (2%)			
Myocardium, inflammation, chronic			1 (2%)	
Myocardium, mineralization	1 (2%)	2 (4%)		
Myocardium, necrosis			1 (2%)	
Pericardium, inflammation, chronic			1 (2%)	
Valve, inflammation				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, focal	1 (2%)	1 (2%)		
Hypertrophy, focal		2 (4%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)	
Subcapsular, hyperplasia	49 (98%)	49 (98%)	50 (100%)	50 (100%)
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	25 (50%)	18 (36%)	20 (40%)	18 (36%)
Parathyroid gland	(39)	(41)	(45)	(46)
Cyst			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Pars distalis, hyperplasia	11 (22%)	3 (6%)	9 (18%)	12 (24%)
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		1 (2%)	
C-cell, hyperplasia				2 (4%)
Follicle, cyst	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Follicular cell, necrosis	1 (2%)			

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(49)	(49)
Cyst	2 (4%)			1 (2%)
Inflammation, suppurative	1 (2%)			
Ovary	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		2 (4%)	
Cyst	27 (54%)	22 (44%)	21 (42%)	25 (50%)
Mineralization				1 (2%)
Thrombosis		1 (2%)	3 (6%)	1 (2%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Thrombosis		1 (2%)	1 (2%)	
Endometrium, hyperplasia, cystic	49 (98%)	48 (96%)	47 (94%)	47 (94%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Myeloid cell, hyperplasia	1 (2%)			
Lymph node	(6)	(7)	(4)	(6)
Deep cervical, hyperplasia, lymphoid		1 (14%)		
Iliac, hyperplasia, lymphoid		1 (14%)	1 (25%)	
Lumbar, hyperplasia, lymphoid	1 (17%)		1 (25%)	
Lumbar, inflammation, acute	1 (17%)			
Mediastinal, hyperplasia, lymphoid	1 (17%)	1 (14%)		2 (33%)
Renal, hyperplasia, lymphoid				1 (17%)
Lymph node, mandibular	(49)	(50)	(50)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid	1 (2%)		2 (4%)	
Lymph node, mesenteric	(50)	(49)	(48)	(48)
Hyperplasia, histiocytic			1 (2%)	
Spleen	(50)	(50)	(49)	(50)
Atrophy	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	32 (64%)	24 (48%)	30 (61%)	33 (66%)
Hyperplasia, lymphoid			1 (2%)	
Thymus	(49)	(49)	(49)	(49)
Atrophy	13 (27%)	17 (35%)	19 (39%)	16 (33%)
Hyperplasia, focal	1 (2%)			
Hyperplasia, histiocytic	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Duct, dilatation	1 (2%)		1 (2%)	
Skin	(50)	(50)	(50)	(50)
Epidermis, hyperkeratosis	1 (2%)			
Epidermis, hyperplasia	1 (2%)			
Epidermis, inflammation, suppurative	1 (2%)			
Epidermis, ulcer	1 (2%)			
Site of application, epidermis, hyperkeratosis	3 (6%)			
Site of application, epidermis, hyperplasia	14 (28%)	50 (100%)	46 (92%)	50 (100%)
Site of application, epidermis, inflammation, suppurative	1 (2%)	2 (4%)	20 (40%)	32 (64%)
Site of application, epidermis, ulcer	1 (2%)	1 (2%)	6 (12%)	17 (34%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Integumentary System (continued)				
Skin (continued)	(50)	(50)	(50)	(50)
Subcutaneous tissue, edema		1 (2%)		
Subcutaneous tissue, fibrosis				1 (2%)
Subcutaneous tissue, inflammation, chronic	1 (2%)			
Subcutaneous tissue, necrosis	1 (2%)			
Subcutaneous tissue, site of application, dermis, inflammation, chronic	4 (8%)	27 (54%)	31 (62%)	44 (88%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis	7 (14%)	6 (12%)	13 (26%)	10 (20%)
Fracture				1 (2%)
Hyperostosis		1 (2%)		
Cranium, callus			1 (2%)	
Femur, hyperostosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(49)	(50)
Cyst epithelial inclusion				1 (2%)
Hydrocephalus			1 (2%)	
Artery, inflammation, chronic			1 (2%)	
Artery, meninges, inflammation, chronic		1 (2%)		
Hypothalamus, compression			3 (6%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, acute	1 (2%)			
Inflammation, chronic	2 (4%)		3 (6%)	1 (2%)
Inflammation, granulomatous	1 (2%)			
Mineralization		2 (4%)		
Alveolar epithelium, hyperplasia, focal			1 (2%)	1 (2%)
Bronchus, hyperplasia, focal	1 (2%)			
Bronchus, hyperplasia, lymphoid	1 (2%)			
Mediastinum, inflammation, chronic			1 (2%)	
Serosa, inflammation, chronic			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	
Sinus, inflammation, suppurative				1 (2%)
Special Senses System				
Eye	(49)	(50)	(50)	(50)
Degeneration	1 (2%)			
Inflammation, chronic		1 (2%)		
Harderian gland	(49)	(50)	(50)	(50)
Hyperplasia	4 (8%)	3 (6%)	4 (8%)	5 (10%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine

	Vehicle Control	100 mg/kg	300 mg/kg	1,000 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis		1 (2%)		
Infarct	1 (2%)	5 (10%)	3 (6%)	3 (6%)
Metaplasia, osseous			1 (2%)	3 (6%)
Nephropathy	24 (48%)	18 (36%)	23 (46%)	20 (40%)
Glomerulus, amyloid deposition		2 (4%)		
Glomerulus, cyst				1 (2%)
Papilla, necrosis	1 (2%)	1 (2%)		1 (2%)
Papilla, renal tubule, atrophy				1 (2%)
Pelvis, inflammation, granulomatous			1 (2%)	
Renal tubule, cyst			1 (2%)	
Renal tubule, cytoplasmic alteration		1 (2%)		
Renal tubule, mineralization				1 (2%)
Urinary bladder	(50)	(50)	(49)	(49)
Cyst				1 (2%)

APPENDIX C
GENETIC TOXICOLOGY

Salmonella typhimurium Mutagenicity Test Protocol 126
Chinese Hamster Ovary Cell Cytogenetics Protocols 126
Drosophila melanogaster Test Protocol 127
Mouse Peripheral Blood Micronucleus Test Protocol 128
Evaluation Protocol 128
Results 129
Table C1 Mutagenicity of Triethanolamine in *Salmonella typhimurium* 130
Table C2 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Triethanolamine 131
Table C3 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Triethanolamine 132
Table C4 Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Triethanolamine 133
Table C5 Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Triethanolamine by Dermal Application for 13 Weeks 133

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Triethanolamine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of triethanolamine. The high dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Triethanolamine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and three doses of triethanolamine. In the trials conducted without S9, the high dose was limited by toxicity; in the trials with S9, the high dose was limited to 10,100 µg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 25.5 to 28 hours with triethanolamine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 to 28 hours, the medium containing triethanolamine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for up to 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with triethanolamine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no triethanolamine. Incubation proceeded for an additional 25.8 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.,* 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with triethanolamine for 8.5 hours; Colcemid was added, and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with triethanolamine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.,* 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Drosophila melanogaster Test Protocol

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Yoon *et al.* (1985). Triethanolamine was supplied as a coded aliquot by Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, triethanolamine was retested by injection into adult males. Three dose levels were tested to ensure adequate testing of the chemical.

To administer triethanolamine by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 µL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of triethanolamine at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a solution of triethanolamine in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of triethanolamine dissolved in saline or peanut oil and allowed to recover for 24 hours. A concurrent saline or peanut oil control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings was treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Clusters were identified in four dose groups in this series of experiments (Table C4). Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.,* 1992) using a normal approximation to the binomial test (Margolin *et al.,* 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 13-week toxicity study (NTP, 1999), peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.,* 1983) and coded. Slides were scanned to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of 10 animals per dose group. In addition, the percentage of polychromatic erythrocytes among 10,000 erythrocytes was determined as a measure of bone marrow toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dosed group is less than or equal to 0.025 divided by the number of dosed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 13-week study were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Triethanolamine (33 to 3,333 µg/plate) was negative for induction of mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with or without S9 metabolic activation (Table C1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured CHO cells, no induction of SCEs (Table C2) or Abs (Table C3) was observed with or without S9 (Galloway *et al*., 1987). In the SCE test without S9, the first of two trials was negative. In the second trial, a significant increase in SCEs was observed at the highest dose tested (2,520 µg/mL), but the trend test was negative ($P \geq 0.025$), and the trial was concluded to be equivocal. Severe cytotoxicity limited the number of cells that could be scored at this dose. Overall, the SCE test was considered to be negative. Cytotoxicity was also noted at the highest dose tested (4,030 µg/mL) in the Abs test without S9.

Triethanolamine administered by feeding or injection at doses up to 30,000 ppm did not induce SLRL mutations in germ cells of male *D. melanogaster* (Table C4; Yoon *et al.*, 1985). Results of an *in vivo* peripheral blood micronucleus test in mice were also negative (Table C5; Witt *et al.*, 2000). In this test, blood samples were obtained from male and female mice after 13 weeks of dermal applications of 1,000 to 4,000 mg/kg triethanolamine. No significant increases in the frequencies of micronucleated NCEs were observed at any dose level, and the percentages of PCEs in the dosed groups were similar to those in the vehicle control groups, indicating an absence of bone marrow toxicity.

Table C1
Mutagenicity of Triethanolamine in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	–S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	89 ± 2.6	104 ± 11.8	192 ± 13.5	163 ± 14.8	159 ± 15.2	164 ± 8.4
	33	96 ± 8.5	112 ± 6.1	180 ± 7.9	145 ± 4.2	162 ± 9.9	143 ± 14.5
	100	87 ± 3.1	98 ± 2.2	215 ± 26.7	162 ± 11.0	151 ± 6.1	157 ± 4.4
	333	74 ± 12.7	93 ± 5.2	188 ± 10.0	154 ± 4.6	165 ± 3.7	147 ± 12.2
	1,000	73 ± 3.2	106 ± 10.6	145 ± 5.2	148 ± 13.6	152 ± 6.1	149 ± 5.4
	3,333	74 ± 4.8	96 ± 5.3	155 ± 3.8	137 ± 2.6	153 ± 14.2	122 ± 20.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		359 ± 21.0	425 ± 29.6	668 ± 41.6	935 ± 188.8	299 ± 30.2	293 ± 1.2
TA1535	0	7 ± 0.9	4 ± 1.3	9 ± 1.5	6 ± 1.5	11 ± 1.9	7 ± 2.0
	33	5 ± 1.7	2 ± 0.3	9 ± 0.9	4 ± 1.2	8 ± 2.2	3 ± 1.2
	100	5 ± 2.1	3 ± 0.3	6 ± 0.9	2 ± 1.2	8 ± 2.3	4 ± 1.0
	333	10 ± 1.5	3 ± 1.5	6 ± 1.8	4 ± 0.0	9 ± 1.5	7 ± 2.1
	1,000	7 ± 0.9	3 ± 0.7	7 ± 1.8	6 ± 0.7	9 ± 1.9	4 ± 1.2
	3,333	7 ± 0.6	4 ± 0.6	8 ± 1.8	3 ± 1.5	8 ± 2.1	5 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		193 ± 19.5	291 ± 39.0	61 ± 11.8	47 ± 7.7	71 ± 4.6	19 ± 2.0
TA1537	0	9 ± 2.4	6 ± 1.5	8 ± 1.5	9 ± 0.3	8 ± 2.0	5 ± 1.8
	33	6 ± 2.2	5 ± 0.7	10 ± 1.3	9 ± 2.5	11 ± 1.8	5 ± 1.2
	100	7 ± 1.2	6 ± 0.6	10 ± 3.0	10 ± 1.0	8 ± 1.2	4 ± 1.2
	333	7 ± 1.2	6 ± 1.3	8 ± 3.5	8 ± 1.3	12 ± 2.5	5 ± 1.7
	1,000	9 ± 0.9	6 ± 0.9	7 ± 2.4	7 ± 1.0	7 ± 0.9	6 ± 0.9
	3,333	3 ± 0.3	5 ± 2.7	9 ± 1.8	8 ± 1.5	9 ± 1.5	8 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		300 ± 35.1	198 ± 22.5	37 ± 10.7	44 ± 3.2	35 ± 5.8	19 ± 1.2
TA98	0	18 ± 2.3	15 ± 2.0	23 ± 2.7	18 ± 2.9	23 ± 1.0	19 ± 2.1
	33	13 ± 1.7	12 ± 2.6	18 ± 1.0	15 ± 1.3	20 ± 3.7	15 ± 1.5
	100	14 ± 2.3	11 ± 0.7	31 ± 9.4	18 ± 3.1	27 ± 1.7	18 ± 3.5
	333	15 ± 1.5	12 ± 0.9	23 ± 4.4	17 ± 0.3	17 ± 1.7	13 ± 2.6
	1,000	9 ± 1.5	12 ± 2.2	25 ± 2.0	19 ± 0.6	18 ± 3.4	15 ± 0.9
	3,333	14 ± 1.9	12 ± 1.2	17 ± 3.5	13 ± 0.9	16 ± 0.7	11 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		261 ± 25.1	245 ± 30.7	330 ± 15.5	420 ± 7.1	94 ± 2.5	166 ± 1.2

[a] The study was performed at Case Western Reserve University. The detailed protocol and these data are presented by Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Triethanolamine[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
–S9								
Trial 1								
Summary: Negative								
Medium[c]		50	1,047	398	0.38	8.0	25.8	
Triethanolamine	100	50	1,050	443	0.42	8.9	25.8	10.99
	330	50	1,050	417	0.39	8.3	25.8	4.47
	1,010	50	1,048	387	0.36	7.7	25.8	–2.86
					P=0.745[d]			
Mitomycin-C[e]	0	50	1,049	1,887	1.79	37.7	25.8	373.22
Trial 2								
Summary: Equivocal								
Medium		50	1,043	435	0.41	8.7	25.5	
Triethanolamine	630	50	1,041	447	0.42	8.9	25.5	2.96
	1,260	50	1,043	438	0.41	8.8	25.5	0.69
	2,520	8	163	84	0.51	10.5	28.0	23.56*
					P=0.174			
Mitomycin-C	0.005	50	1,036	1,648	1.59	33.0	25.5	281.42
+S9								
Summary: Negative								
Medium		50	1,034	426	0.41	8.5	25.8	
Triethanolamine	330	50	1,031	446	0.43	8.9	25.8	5.00
	1,010	50	1,045	453	0.43	9.1	25.8	5.22
	10,100	50	1,039	463	0.44	9.3	25.8	8.16
					P=0.130			
Cyclophosphamide[e]	1.5	50	1,039	1,389	1.33	27.8	25.8	224.49

* Positive response (≥20% increase over solvent control)
a The study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
b SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
c Solvent control
d Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose
e Positive control

Table C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Triethanolamine[a]

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
–S9					
Trial 1					
Harvest time: 10.5 hours					
Summary: Negative					
Dimethylsulfoxide[b]		100	7	0.07	5.0
Triethanolamine	1,510	100	2	0.02	2.0
	2,010	100	1	0.01	1.0
	4,030	56	0	0.00	1.0
					P=0.985[c]
Mitomycin-C[d]	0.5	100	24	0.24	20.0
+S9					
Trial 1					
Harvest time: 10.5 hours					
Summary: Negative					
Dimethylsulfoxide		100	2	0.02	2.0
Triethanolamine	6,040	100	3	0.03	3.0
	8,060	100	6	0.06	5.0
	10,070	100	2	0.02	2.0
					P=0.373
Cyclophosphamide[d]	25	100	32	0.32	26.0

[a] Study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987).
[b] Solvent control
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[d] Positive control

Table C4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Triethanolamine[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Feeding	20,000[c]	2	3	0/1,011	1/1,262	1/570	2/2,843 (0.07%)
	0[c]			1/909	2/1,467	1/735	4/3,111 (0.13%)
	30,000	48	20	0/1,190	1/1,924	0/739	1/3,853 (0.03%)
	0[c]			2/2,091	2/2,509	2/1,989	6/6,589 (0.09%)
Injection	10,000	12	0	0/1,016	0/1,185	2/1,000	2/3,201 (0.06%)
	0[c]			0/1,024	0/1,179	0/981	0/3,184 (0.00%)
	20,000	8	0	0/524	0/1,127	1/984	1/2,635 (0.04%)
	0			0/374	0/1,268	2/871	2/2,513 (0.08%)
	30,000	56	30	1/247	0/113	1/108	2/468 (0.43%)
	0			1/864	2/1,078	1/1,091	4/3,033 (0.13%)

[a] The study was performed at Brown University. The detailed protocol and these data are presented by Yoon *et al.* (1985). The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al.*, 1992). Results were not significant at the 5% level (Margolin *et al.*, 1983).
[b] Total number of lethal mutations/number of X chromosomes tested for three mating trials
[c] Data were corrected for the occurrence of spontaneous clusters.

Table C5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Triethanolamine by Dermal Application for 13 Weeks[a]

Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/1,000 NCEs[b]	P Value[c]	PCEs (%)
Male				
Vehicle control	10	1.75 ± 0.20		2.2
1,000	10	1.88 ± 0.17	0.3138	2.2
2,000	10	1.36 ± 0.10	0.9350	2.4
4,000	10	1.90 ± 0.30	0.3047	2.1
		P=0.420[d]		
Female				
Vehicle control	10	1.16 ± 0.12		2.1
1,000	10	1.20 ± 0.08	0.3890	2.2
2,000	10	1.08 ± 0.12	0.7393	2.2
4,000	10	0.99 ± 0.11	0.8813	2.0
		P=0.925		

[a] The detailed protocol is presented by MacGregor *et al*. (1990), and these data are presented by Witt *et al*. (2000). NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle controls, significant at $P \leq 0.008$ (ILS, 1990)
[d] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at $P \leq 0.025$ (ILS, 1990)

APPENDIX D
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization 136
Preparation and Analysis of Dose Formulations 137
Figure D1 Infrared Absorption Spectrum of Triethanolamine 138
Figure D2 Nuclear Magnetic Resonance Spectrum of Triethanolamine 139
Table D1 Gas Chromatography Systems Used in the 2-Year Dermal Study of Triethanolamine 140
Table D2 High-Performance Liquid Chromatography Systems Used in the 2-Year Dermal Study of Triethanolamine 141
Table D3 Preparation and Storage of Dose Formulations in the 2-Year Dermal Study of Triethanolamine 141
Table D4 Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Triethanolamine 142

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Triethanolamine

Triethanolamine was obtained from Texaco Chemical Company (Division of Texaco, Inc., Bellaire, TX) in one lot (7G-60) for use during the 2-year study. Identity, purity, and moisture content analyses were conducted by the analytical chemistry laboratory (Research Triangle Institute, Research Triangle Park, NC); identity, purity, and stability analyses were conducted by the study laboratory. Special analyses of diethanolamine and nitrosamine impurities in the bulk chemical were conducted by the analytical chemistry laboratory and Covance Laboratories, Inc. (Madison, WI), respectively. Reports on analyses performed in support of the triethanolamine study are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as triethanolamine by the analytical chemistry laboratory using ultraviolet/visible, infrared, and proton nuclear magnetic resonance (NMR) spectroscopy and high- and low-resolution mass spectrometry and by the study laboratory using infrared spectroscopy. All spectra were consistent with the structure of triethanolamine and with the literature spectra (*Aldrich*, 1981, 1983, 1993; *NIST Standard Reference Database*). The observed mass of the high-resolution mass spectrometry base peak was within acceptable limits of the calculated mass. The infrared and NMR spectra are presented in Figures D1 and D2.

The moisture content of lot 7G-60 was determined by Galbraith Laboratories, Inc. (Knoxville, TN) using Karl Fischer titration. The purity of lot 7G-60 was determined by the analytical chemistry laboratory (systems A, B, and C) and the study laboratory (system D) using gas chromatography with flame ionization detection (Table D1). Purity of lot 7G-60 was also determined by the analytical chemistry laboratory using high-performance liquid chromotography (HPLC) with photodiode array detection (system 1; Table D2).

Karl Fischer titration indicated 0.18% water. Gas chromatography using systems B and D indicated one major peak and no impurities. Gas chromatography using system A indicated one major peak and one impurity with an area of 0.88% relative to the major peak area; the impurity was determined to be diethanolamine. Gas chromatography using system C indicated that the compound contained no impurity other than diethanolamine at a concentration greater than 0.1%. HPLC using system 1 indicated no measurable impurities with chromophores in a triethanolamine solution scanned for 30 minutes from 200 to 400 nm. The overall purity of lot 7G-60 was determined to be greater than 99%.

A special HPLC/mass spectrometric study was conducted by the analytical chemistry laboratory using system 2 (Table D2) to determine the relative concentration of diethanolamine as an impurity in the test chemical (lot 7G-60), and to conduct an accelerated stability study. A low resolution electrospray ionization detector was used in the mass spectrometer. Analysis showed that diethanolamine constituted 0.491% (weight percent relative to the test chemical weight) of the test chemical. Solutions of triethanolamine were prepared in acetone or 95% ethanol at approximately 500 mg/mL for the accelerated stability study. Aliquots of the solutions were stored in sealed glass containers at 32° to 36° C, protected from light, for 1.6 hours or 11 days. After 11 days of storage, both solutions showed slight increases in diethanolamine concentrations compared to those measured at time 0; no differences were noted following 1.6 hours of storage.

The concentrations of nonpolar nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitrosodi-n-propylamine, *N*-nitrosodi-n-butylamine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, and *N*-nitrosomorpholine) and the polar nitrosamine *N*-nitrosodiethanolamine in triethanolamine, lot 7G-60, were determined by Covance Laboratories, Inc. Nonpolar nitrosamines were analyzed

by gas chromatography (system E), and the polar nitrosamine *N*-nitrosodiethanolamine was analyzed by HPLC (system 3); both systems used a thermal energy analyzer for detection. No nonpolar or polar nitrosamines were present at concentrations greater than the limits of detection (0.1 and 1.0 ppm, respectively).

Stability studies of the bulk chemical were performed on lot 03601CN (not used in the current study) by the study laboratory using gas chromatography with flame ionization detection (system F). Triethanolamine was stable for 14 days when stored in amber glass vials at 5°, 25°, and 60° C, when compared to a sample stored at –20°C. To ensure stability, triethanolamine was stored at room temperature in amber glass containers with Teflon®-lined lids. No degradation of triethanolamine was observed.

Acetone

Acetone was obtained in four lots (NE0173, NV0163, OG0513, and OX0312) from Spectrum Chemical Manufacturing Corporation (Gardena, CA) for use during the 2-year study. Identity and purity analyses of each lot were conducted by the study laboratory.

The chemical, a clear liquid, was identified as acetone using infrared spectroscopy. The purity of each lot was determined using gas chromatography with flame ionization detection (system G). No significant impurities were detected in any lot. The overall purity of each lot was determined to be greater than 99%.

To ensure stability, the bulk chemical was stored at room temperature in amber glass bottles. No degradation of the acetone was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared approximately every 2 weeks by mixing triethanolamine and acetone to give the required concentration (Table D3). The dose formulations were stored for up to 21 days at 5° C in amber glass bottles with Teflon®-lined lids.

Stability studies of 10 mg/mL dose formulations in acetone were performed by Midwest Research Institute (Kansas City, MO) using gas chromatograpy with flame ionization detection (system H). The stability of the dose formulations was confirmed for at least 3 weeks when stored at room temperature in sealed amber glass vials under a nitrogen headspace, and for at least 3 hours under animal room conditions (open to air and light).

Periodic analyses of the dose formulations of triethanolamine were conducted by the study laboratory with gas chromatography using system D. During the 2-year study, the dose formulations were analyzed approximately every 8 or 12 weeks (Table D4); animal room samples were also analyzed periodically. Of the dose formulations analyzed, all 66 were within 10% of the target concentrations; 18 of 24 animal room samples were within 10% of the target concentrations.

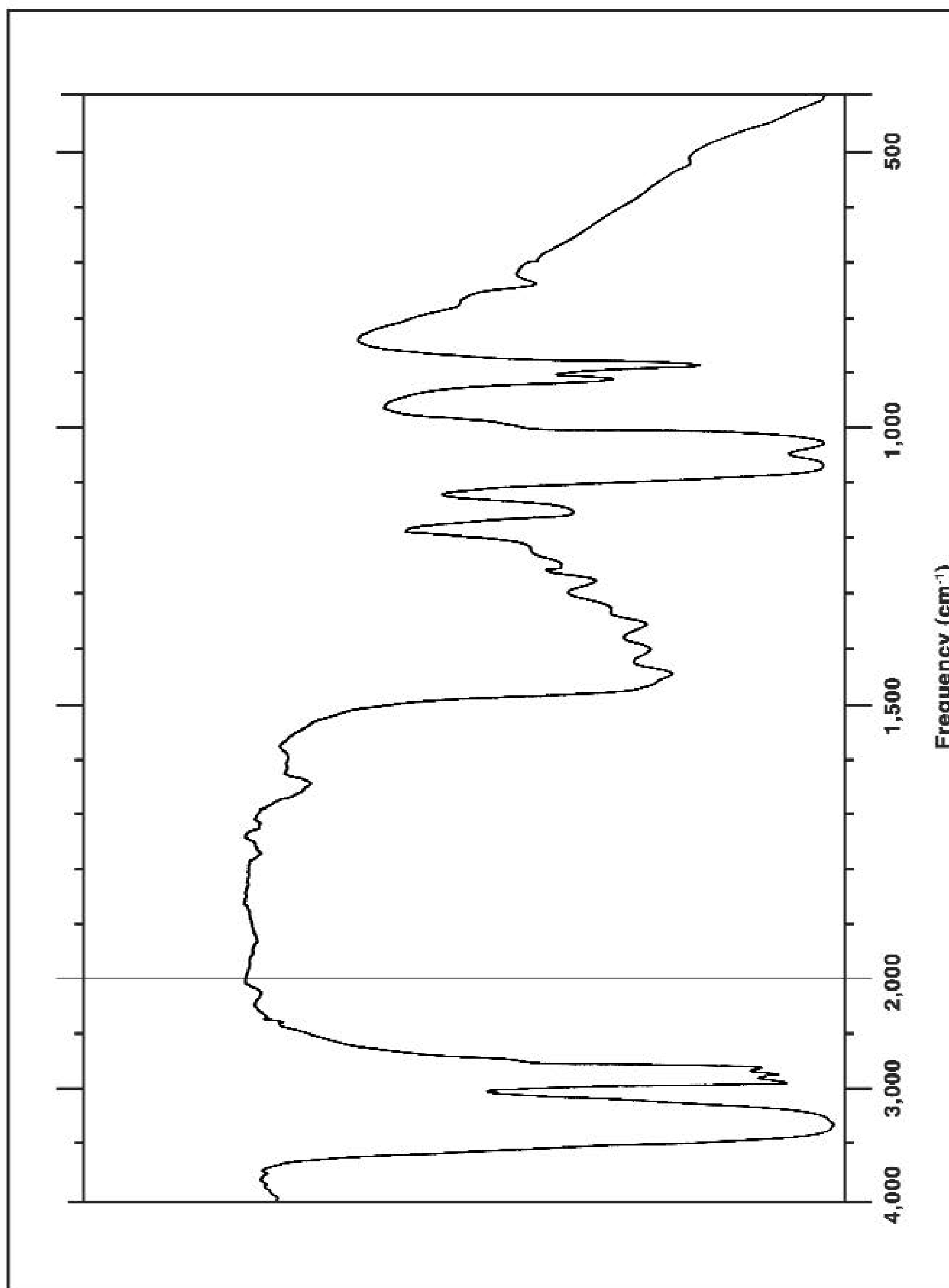

FIGURE D1
Infrared Absorption Spectrum of Triethanolamine

N

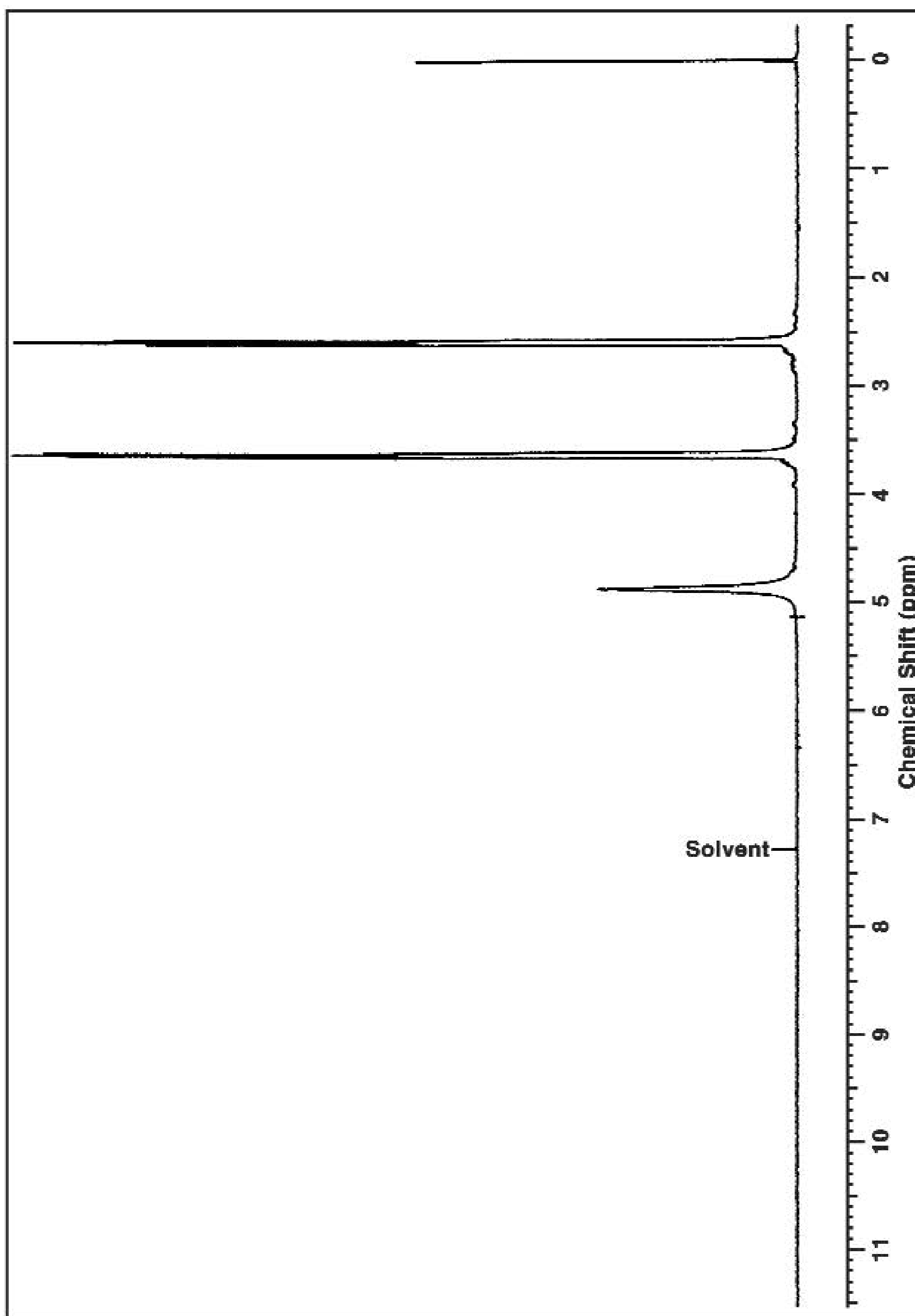

FIGURE D2
Nuclear Magnetic Resonance Spectrum of Triethanolamine

Table D1
Gas Chromatography Systems Used in the 2-Year Dermal Study of Triethanolamine[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	Capillary, Supelco Carbowax Amine, 30 m × 0.53 mm, 1.0-µm film thickness (Supelco, Bellefonte, PA)	Helium at 2.1 mL/minute	35° C for 1 minute, then 10° C/minute to 280° C, held 13.5 minutes
System B			
Flame ionization	Packed, Supelco Tenax, 1.8 m × 0.25 inches, 60/80 mesh	Helium at 33.5 mL/minute	150° C to 300° C at 10° C/minute, held 25 minutes
System C			
Flame ionization	Capillary, Supelco Carbowax Amine (30 m × 0.53 mm, 1.0-µm film thickness	Helium at 10 mL/minute	60° C for 1 minute, then 20° C/minute to 200° C, held 32 minutes
System D			
Flame ionization	Packed, Supelco Tenax TA or GC 60/80 mesh, 1.8 m × 2 mm	Helium at approximately 15 mL/minute	220° C to 280° C at 10° C/minute, held 4 minutes
System E			
Thermal energy analyzer	Packed 10% Carbowax 1540 100/120 mesh WHP in 5% KOH, 6 ft × 4 mm	Argon at 25 mL/minute	120° C for 4 minutes, then 4° C/minute to 180° C, held for 8 minutes
System F			
Flame ionization	Packed, Supelco Tenax TA, 60/80 mesh, 6 ft × 2 mm	Helium at 15 mL/minute	220° C for 7 minutes, then 10° C/minute to 260° C, held for 6 minutes
System G			
Flame ionization	Packed 20% SP-2401/0.1% Carbopack 1500 on 100/120 Supelcoport, 2.4 m × 2mm	Helium at 30 mL/minute	50° C for 4 minutes, then 10° C/minute to 170° C
System H			
Flame ionization	Capillary, Supelco DB-1, 15 m × 0.51 mm, 1.5-µm film thickness	Helium at 26 mL/minute	80° C for 5 minutes, then 15° C/minute to 190° C, held for 3 minutes

[a] Gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA) (systems A, B, C, E, and G), Varian (Palo Alto, CA) (system H).

Table D2
High-Performance Liquid Chromatography Systems Used in the 2-Year Dermal Study of Triethanolamine[a]

Detection System	Column	Solvent System
System 1		
Photodiode array (200 to 400 nm scan)	Hamilton PRP-X200, 15 cm × 4.1 mm (Hamilton Co., Reno, NV)	4.0 mM nitric acid:methanol (70:30), 1.0 mL/minute
System 2		
Low resolution mass spectrometry with electrospray ionization	Agilent/ZORBAX 300-SCX, 15 cm × 2.1 mm, 5 µm particle size (Agilent Technologies, Palo Alto, CA)	Water with trifluoroacetic acid (TFA) (10 mM) to methanol:water (90:10) with TFA (10 mM) in 15 minutes, held for 3 minutes, flow rate 0.3 mL/minute
System 3		
Thermal energy analyzer	Alltech Platinum CN, 25 cm × 2.1 mm, 5 µm particle size (Alltech Associates, Inc., Deerfield, IL)	Isooctane:dichloromethane:methanol (71:18:11), 0.4 mL/minute

[a] The high-performance liquid chromatographs were manufactured by Waters, Inc. (Milford, MA) (system 1), Agilent, Inc. (Palo Alto, CA) (system 2), and Hewlett-Packard (Palo Alto, CA) (system 3). The mass spectrometer used in system 2 was manufactured by PerkinElmer, Inc. (Shelton, CT).

Table D3
Preparation and Storage of Dose Formulations in the 2-Year Dermal Study of Triethanolamine

Preparation
Dose formulations were prepared by mixing triethanolamine with acetone. Dose formulations were prepared every 2 weeks.

Chemical Lot Number
7G-60

Maximum Storage Time
21 days

Storage Conditions
Stored in amber glass bottles with Teflon®-lined lids at 5° C

Study Laboratory
Battelle Columbus Laboratories (Columbus, OH)

Table D4
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Triethanolamine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
September 14, 1998	September 16, 1998	50	54.80	+10
		100	101.7	+2
		150	153.5	+2
		315	326.8	+4
		500	512.2	+2
		1,000	1,041	+4
	October 7, 1998[b]	50	62.33	+25
		100	114.4	+14
		150	171.7	+14
		315	350.5	+11
		500	557.8	+12
		1,000	1,096	+10
November 9, 1998	November 10, 1998	50	50.65	+1
		100	99.15	–1
		150	148.6	–1
		315	320.5	+2
		500	505.3	+1
		1,000	1,029	+3
February 1, 1999	February 1, 1999	50	48.85	–2
		100	99.77	0
		150	151.5	+1
		315	316.5	0
		500	509.7	+2
		1,000	1,005	+1
	February 23-24, 1999[b]	50	54.93	+10
		100	107.3	+7
		150	160.5	+7
		315	337.8	+7
		500	534.2	+7
		1,000	1,020	+2
March 29, 1999	April 1, 1999	50	48.55	–3
		100	99.63	0
		150	149.8	0
		315	324.5	+3
		500	503.2	+1
		1,000	1,022	+2
June 21, 1999	June 22, 1999	50	51.85	+4
		100	101.7	+2
		150	153.7	+2
		315	325.2	+3
		500	512.0	+2
		1,000	967.3	–3

Table D4
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Triethanolamine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
August 16, 1999	August 17, 1999	50	53.18	+6
		100	101.1	+1
		150	153.6	+2
		315	326.1	+4
		500	514.2	+3
		1,000	1,037	+4
	September 7, 1999[b]	50	54.10	+8
		100	108.1	+8
		150	160.8	+7
		315	342.6	+9
		500	530.1	+6
		1,000	1,009	+1
November 8, 1999	November 10, 1999	50	52.62	+5
		100	101.2	+1
		150	150.6	0
		315	322.2	+2
		500	508.8	+2
		1,000	1,014	+1
January 4, 2000	January 5-6, 2000	50	47.38	–5
		100	95.57	–4
		150	145.2	–3
		315	311.4	–1
		500	488.4	–2
		1,000	1,023	+2
March 27, 2000	March 31-April 1, 2000	50	51.73	+3
		100	97.52	–2
		150	149.3	0
		315	316.6	+1
		500	511.2	+2
		1,000	961.0	–4
	April 18, 2000[b]	50	58.42	+17
		100	105.4	+5
		150	159.2	+6
		315	331.4	+5
		500	525.5	+5
		1,000	1,054	+5
May 22, 2000	May 23-24, 2000	50	49.96	0
		100	103.8 ± 4.6[c]	+4
		150	155.7	+4
		315	343.7	+9
		500	524.3	+5
		1,000	1,033	+3

Table D4
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Triethanolamine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
August 14, 2000	August 15, 2000	50	51.63	+3
		100	100.6	+1
		150	152.4	+2
		315	312.8	–1
		500	499.8	0
		1,000	1,005	+1

[a] Results of duplicate analyses. 50 mg/mL=100 mg/kg; 100 mg/mL=200 mg/kg; 150 mg/mL=300 mg/kg; 315 mg/mL=630 mg/kg; 500 mg/mL=1,000 mg/kg; 1,000 mg/mL=2,000 mg/kg
[b] Animal room samples
[c] Due to poor agreement between the duplicates originally analyzed, two additional replicates were prepared and analyzed; the reported values are the average ± standard deviation of the four replicates.

APPENDIX E
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE E1 Ingredients of NTP-2000 Rat and Mouse Ration 146
TABLE E2 Vitamins and Minerals in NTP-2000 Rat and Mouse Ration 146
TABLE E3 Nutrient Composition of NTP-2000 Rat and Mouse Ration 147
TABLE E4 Contaminant Levels in NTP-2000 Rat and Mouse Ration 148

Table E1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

Table E2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

Table E3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.5 ± 0.44	12.7 – 14.5	24
Crude fat (% by weight)	8.1 ± 0.25	7.6 – 8.6	24
Crude fiber (% by weight)	9.2 ± 0.67	7.9 – 10.5	24
Ash (% by weight)	5.0 ± 0.20	4.7 – 5.4	24
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,733 ± 924	4,220 – 7,790	24
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	7.9 ± 0.73	6.3 – 9.2	24
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)[b]	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	0.999 ± 0.045	0.903 – 1.090	24
Phosphorus (%)	0.563 ± 0.029	0.505 – 0.618	24
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

Table E4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± StandardDeviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.17 ± 0.081	0.10 – 0.37	24
Cadmium (ppm)	0.04 ± 0.007	0.04 – 0.07	24
Lead (ppm)	0.11 ± 0.106	0.05 – 0.54	24
Mercury (ppm)	<0.02		24
Selenium (ppm)	0.19 ± 0.035	0.14 – 0.28	24
Aflatoxins (ppb)	<5.00		24
Nitrate nitrogen (ppm)[c]	10.8 ± 3.04	9.04 – 21.1	24
Nitrite nitrogen (ppm)[c]	<0.61		24
BHA (ppm)[d]	<1.0		24
BHT (ppm)[d]	<1.0		24
Aerobic plate count (CFU/g)	10.0 ± 2.0	10.0 – 20.0	24
Coliform (MPN/g)	0.30 ± 1.0	0.0 – 3.6	24
Escherichia coli (MPN/g)	<10		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[e]	4.5 ± 1.56	2.1 – 8.8	24
N-Nitrosodimethylamine (ppb)[e]	1.8 ± 0.88	1.0 – 5.1	24
N-Nitrosopyrrolidine (ppb)[e]	2.6 ± 1.00	1.0 – 5.6	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Pesticides (ppm)			
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl chlorpyrifos	0.145 ± 0.123	0.023 – 0.499	24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.207 ± 0.190	0.020 – 0.826	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: Alfalfa, grains, and fish meal
[d] Sources of contamination: Soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX F
SENTINEL ANIMAL PROGRAM

Methods 150
Results 150

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected mice during the 2-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to MABioservices/BioReliance Corporation (Rockville, MD) for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the study are also listed.

Method and Test	Time of Analysis
Bacterial Assays	
Oral	18 months
Fecal [including PCR (polymerase chain reaction) analysis for *Helicobacter hepaticus sp.*]	18 months
ELISA	
Ectromelia virus	1, 5, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	1, 5, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	1, 5, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	1, 5, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 5, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	1, 5, 12, and 18 months, study termination
Mycoplasma arthritidis	18 months, study termination
Mycoplasma pulmonis	18 months, study termination
PVM (pneumonia virus of mice)	1, 5, 12, and 18 months, study termination
Reovirus 3	1, 5, 12, and 18 months, study termination
Sendai	1, 5, 12, and 18 months, study termination
Immunofluorescence Assay	
Ectromelia virus	Study termination
GDVII	18 months
LCM	18 months
Mouse adenoma virus-FL	12 and 18 months
MCMV (mouse cytomegalovirus)	18 months, study termination
MHV	5 months, study termination
Parvovirus	1, 5, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX G
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION STUDIES

Introduction 152
Materials and Methods 152
Results and Discussion 154
Summary 155
References 155
Table G1 Excretion of Radioactivity by Female Rats Following an Intravenous Dose of [^{14}C]-Triethanolamine 157
Table G2 Distribution of Radioactivity in Tissue of Female Rats Following an Intravenous Dose of [^{14}C]-Triethanolamine 157
Table G3 Excretion of Radioactivity by Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine 158
Table G4 Distribution of Radioactivity in Tissue of Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine 159
Table G5 Distribution of Absorbed and Unabsorbed Radioactivity in Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine 160
Table G6 Excretion of Radioactivity by Female Mice Following an Intravenous Dose of [^{14}C]-Triethanolamine 161
Table G7 Distribution of Radioactivity in Tissue of Female Mice Following an Intravenous Dose of [^{14}C]-Triethanolamine 161
Table G8 Excretion of Radioactivity by Female Mice Following Dermal Administration of [^{14}C]-Triethanolamine 162
Table G9 Distribution of Absorbed and Unabsorbed Radioactivity in Female Mice Following Dermal Administration of [^{14}C]-Triethanolamine 162
Figure G1 Radiochromatogram of Urine from Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine 163

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION STUDIES

Introduction

Triethanolamine is used extensively as an ingredient or chemical intermediate in detergents, cosmetic products, agrichemicals, and cutting oils and as a vulcanization accelerator in rubber manufacturing. The reported annual production of triethanolamine in the United States during 1991 was 86 million kilograms (USITC, 1993). In the presence of nitrosating agents, triethanolamine may be converted to *N*-nitrosodiethanolamine (CIR, 1983), a known liver, kidney, and nasal carcinogen in laboratory animals (Hoffman *et al.*, 1982; Preussman *et al.*, 1982; Lijinsky and Kovatch, 1985).

Triethanolamine is absorbed through the skin and gastrointestinal tract. In mice administered a single 1,000 mg/kg dermal dose of triethanolamine, approximately 60% of the radioactivity was recovered in the urine and 20% in the feces 48 hours after dosing (Melnick and Tomaszewski, 1990). Urinary radioactivity was composed mostly of parent compound. Orally administered triethanolamine was rapidly absorbed and excreted mostly in the urine as the parent compound along with a small amount of the glucuronide (Kohri *et al.*, 1982).

The purpose of this study was to provide absorption, distribution, metabolism, and excretion data for [^{14}C]-triethanolamine in the test animals used in the toxicity testing of triethanolamine by the NTP.

Materials and Methods

Study Design

Groups of four female rats received a single intravenous dose of 3 mg/kg [^{14}C]-triethanolamine or a single dermal dose of 68 or 276 mg/kg. Groups of four female mice received a single intravenous dose of 3 mg/kg [^{14}C]-triethanolamine or a single dermal dose of 79 or 1,120 mg/kg. Expired radioactivity was trapped and quantitated and urine and feces were collected from all F344/N rats and B6C3F$_1$ mice dosed intravenously up to 72 hours after dosing, and urine and feces were collected from all F344/N rats and B6C3F$_1$ mice dosed via skin painting up to 72 hours after dosing. Tissue samples from all intravenous animals and all dermal rats 72 hours after dosing were also examined, and the skin site of application from all dermal mice was examined.

Procurement and Characterization of Radiolabeled and Nonradiolabeled Triethanolamine

[1,2-^{14}C]-Triethanolamine was obtained from Chemsyn Science Laboratories (Lenexa, KS) in one lot (CSL-96-663-38-35). The radiochemical preparation (6 mCi) was supplied in a flame-sealed ampoule solution in ethanol at a concentration of 1.37 mCi/mL. The specific activity of [^{14}C]-triethanolamine was 13.8 mCi/mmol. The radiochemical purity of [^{14}C]-triethanolamine was determined by high performance liquid chromatography (HPLC) and was 97% pure. The chromatographic system consisted of a Whatman Partisil 10 SCX column (250 × 4.6 mm) and a mobile phase of 0.1 M citrate with 5% sodium dihydrogen citrate; the flow rate was 1 mL/minute. Column effluent was monitored with a β-RAM radioactivity detector with a 500 µL solid scintillant flow cell. Following the injection of [^{14}C]-triethanolamine, the column effluent was collected in fractions, and the radioactivity eluting in each fraction was measured by liquid scintillation spectrometry.

Nonradiolabeled triethanolamine was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI) in one lot (05601PN) and stored within secondary containers with solid sodium hydroxide to minimize uptake of acidic gases. The identity of the nonradiolabeled triethanolamine was confirmed by mass spectrometry and proton nuclear magnetic resonance spectroscopy.

Preparation and Administration of Dose Formulations

Single intravenous doses contained approximately 47 µCi radiolabel for rats, approximately 6 µCi radiolabel for mice, an appropriate amount of nonradiolabeled triethanolamine, and isotonic saline as a vehicle that delivered a total dosing volume of 1 mL/kg to rats and 2 mL/kg to mice. Intravenous doses were drawn into a syringe equipped with a Teflon®-tipped plunger (Hamilton) and a 27 (rats) or 30 (mice) gauge hypodermic needle. Excess dose formulation was wiped off the needle before weighing the filled dosing syringe. Intravenous doses were injected into one lateral tail vein. After dosing, the needle was wiped clean with a Kimwipe®, and the empty syringe was reweighed. The Kimwipe® was placed into a vial containing 2 mL ethanol and analyzed by liquid scintillation spectrometry. Each dose was calculated as the difference between the weights of the filled and empty dosing apparatus less the amount found in the Kimwipe®. To determine the concentration of [^{14}C]-triethanolamine in the dose formulation, two weighed aliquots were taken before, two after, and one during dosing.

Dermal doses were formulated in acetone and contained 65 µCi radiolabel for rats and 12 to 15 µCi for mice with an appropriate amount of nonradiolabeled triethanolamine in a volume of approximately 190 µL per dose. A dose area of 12 cm^2 for rats and 1.44 cm^2 for mice was located on each animal's back. Approximately 24 hours prior to dosing, rats were anesthetized with 7:1 ketamine:xylazine (60 mg/kg) by intramuscular injection and mice with sodium pentobarbitol (60 mg/kg) by intraperitoneal injection. Fur at the dose area was clipped with a No. 40 blade (Oster Professional Products). The clipped area on each animal was wiped with a gauze soaked with acetone, dried, and then examined for abrasions. Any animal with abrasions in the clipped area was excluded from the study. The dose area was outlined on the animal's back with a permanent marker, and the animal was placed in a metabolism cage.

Prior to dermal dosing, a protective foam appliance was glued to each rat's back using Hollister's Medical Adhesive. The doses were administered evenly over the dose area using a 500 µL syringe equipped with a Teflon®-tipped plunger and a gavage needle. A nonocclusive cloth cover was attached to the appliance, and a protective metal mesh cover was secured over the appliance with Elastoplast adhesive bandage prior to returning the rat to its cage. The doses for mice were administered over the dose area using a 100 or 250 µL syringe equipped with a Teflon®-tipped plunger and a gavage needle. A metal tissue capsule was glued in place over the dose area using Duro Quick Gel™ Super Glue. The doses were measured and quantitated as described above.

Biological Sample Collection in the Disposition Studies

Urine and feces from rats and mice were collected separately into round-bottom flasks cooled with dry ice at 6 (urine only), 24, 48, and 72 hours after dosing. The samples were stored in the dark at –20° C until analysis.

Radiolabeled components in breath were collected by passing air from the metabolism cage (flow rate of 200 to 500 mL/minute) through two cold traps, each containing 100 mL of ethanol, and then through a series of two traps, each containing 400 mL of 1 N sodium hydroxide. The first cold trap was maintained at 0° C by an ice/water bath, and the second at –60° C by an isopropanol/dry ice bath. Traps were changed at 6, 24, 32, 48, and 56 hours, and the total weight of the solutions was measured.

At the end of the intravenous studies, rats were anesthetized with 7:1 ketamine:xylazine (60 mg/kg) by intramuscular injection, and mice were anesthetized with 60 mg/kg sodium pentobarbital by intraperitoneal injection. Blood was drawn by cardiac puncture into heparinized syringes, and rats and mice were sacrificed. Samples of adipose tissue, muscle, skin, and the entire brain, heart, kidney, liver, lung, and spleen were removed and assayed for [^{14}C] content.

At the end of the dermal studies, rats and mice were anesthetized, blood was drawn, animals were sacrificed, and tissue samples from rats were taken as described above. With the appliance still attached, the dose site skin from rats and mice was excised, with care taken not to remove muscle or adipose tissue. The elastoplast was removed and placed in a bag. For the rat study, the appliance, including the cloth cover, was removed from the dose site

skin. The cloth cover was removed from the appliance and was analyzed separately by liquid scintillation spectrometry. For the mouse study, the metal appliance was removed from the skin using acetone to dissolve the adhesive and then placed in a vial that contained water. The dose site was thoroughly rinsed with ethanol then washed using cotton gauze soaked with soapy water. Next, the skin was rinsed with water-soaked gauze, and all rinses were collected. The gauze was placed into individual scintillation vials for analysis by liquid scintillation spectrometry. The dose site skin was dissolved in 2 N ethanolic sodium hydroxide.

Analysis of Biological Samples for Total Radioactivity

Aliquots of urine, trapping solution from the breath traps, skin wash, mouse appliance collection, and all dose site digests were added directly to vials that contained scintillation cocktail (Ultima Gold, Packard Instrument Company). Samples of tissue, feces, and blood (0.1 to 0.3 g) were digested in Soluene –350 (2 mL). After digestion, samples that required bleaching were decolorized with perchloric acid/hydrogen peroxide prior to addition of the scintillation cocktail. Ultima Gold and either water or ethanol were added to the rat appliance and all skin gauze samples before analysis by liquid scintillation spectrometry.

Analysis of Biological Samples by HPLC

Urine samples were filtered through an Alltech 0.45 µm PTFE syringe filter unit prior to analysis by HPLC. The HPLC system consisted of a Whatman Partisil 10 SCX analytical column with a mobile phase of 0.1 M citric acid/5% sodium dihydrogen citrate buffer that contained 0.1 M sodium chloride and a flow rate of 1 mL/minute. Analytes eluting from the column were detected using a β-RAM Flow-Through Radioactivity Detector equipped with a 600 µL solid scintillate flow cell. After the metabolite profile was established, urine and isolated metabolite peak fractions were incubated overnight at 37° C with purified β-glucoronidase (Sigma, 300 U from *Escherichia coli*). The samples were later analyzed with HPLC using the system described above.

Results and Discussion

Data for the disposition of a 3 mg/kg intravenous dose in female rats are presented in Table G1. The radioactivity was rapidly excreted in the urine, and 90% of the dosed radioactivity was recovered in the urine within 24 hours. An average of 98% of the dose was recovered in the urine within 72 hours after dosing, and approximately 0.6% of the radioactivity was recovered in the feces during this time. Less than 0.5% of the dose was recovered in carbon dioxide traps, and less than 0.1% was recovered in volatiles traps.

The distribution of radioactivity present in tissue samples from female rats is presented in Table G2. Only 0.9% of the dose remained in the tissues 72 hours after dosing. In contrast to diethanolamine, which was only slowly excreted (30% of dose within 48 hours) and accumulated in the brain, heart, kidney, spleen (5% of dose at 48 hours), and liver (27% of dose at 48 hours) in a process thought to involve biochemical mimicry with the natural alkanolamine ethanolamine (Mathews *et al.*, 1995), comparatively little triethanolamine bioaccumulated in the tissues.

Data for the excretion of radioactivity following dermal administration of 68 and 276 mg/kg [^{14}C]-triethanolamine in female rats is presented in Table G3, and the distribution of equivalents present in tissues 72 hours after dosing is presented in Table G4. Approximately 20% to 30% of the dose was absorbed within 72 hours following dermal exposure. The mean percentage of dose absorbed increased with increasing dose, but the increase was not statistically significant (Table G5).

The disposition of a 3 mg/kg intravenous dose in female mice is presented in Table G6. With only 40% of the dose excreted within 24 hours, mice appeared to excrete intravenously administered triethanolamine much slower than did rats (90% in 24 hours; Table G1). Less than 0.5% of the dose was recovered in carbon dioxide traps, and less than 0.1% was recovered in volatiles traps.

The distribution of radioactivity present in tissue samples from female mice is presented in Table G7. As was the case for rats, the heart, kidney, liver, lung, and spleen contained higher concentrations of triethanolamine equivalents relative to blood.

Mice absorbed dermally applied 79 and 1,120 mg/kg triethanolamine more readily than did rats (Tables G8 and G9). Mice rapidly excreted the absorbed radioactivity in the urine and feces with 28% to 48% of the dose recovered in excreta within 24 hours. The percent of the dose absorbed increased with increasing dose.

Urine collected 6 to 24 hours after intravenous dosing and 48 to 72 hours after dermal application of triethanolamine in female rats was analyzed by HPLC (Figure G1). The chromatogram contains a peak that coelutes with triethanolamine and two other peaks that comprise about 5% of the radioactivity in the sample. These peaks, however, were also present in the chromatogram of the radiolabeled test article and may reflect the presence of impurities rather than metabolites. The metabolite fractions were collected and incubated with purified β-glucuronidase, as was an aliquot of the whole urine. Analysis of these samples showed no change in the metabolite profile. Similarly, urine collected 6 to 24 hours after intravenous or dermal dosing contained more than 95% radiolabeled components that coeluted with unchanged triethanolamine, with minor components eluting in the same fractions in mice as those in rats.

Summary

Intravenously administered triethanolamine was rapidly excreted by female rats and mice, primarily in the urine. Less than 1% of the dose was present in tissues sampled 72 hours after dosing. In both species, the heart, kidney, liver, lung, and spleen contained higher concentrations of triethanolamine equivalents than did blood.

Only 20% to 30% of dermally applied 68 and 276 mg/kg triethanolamine was absorbed by female rats within 72 hours. Mice absorbed dermally applied 79 and 1,120 mg/kg triethanolamine more extensively (60% to 80%) than did rats. On the basis of mass of triethanolamine per area of skin, the lowest dermal dose levels for rats and mice were equal at 1.09 mg/cm^2. The skin of mice is thinner than that of rats, and this difference may explain the higher percentage of dose absorbed by mice. The highest dermal doses were 4 and 15 mg/cm^2 for rats and mice, respectively. Triethanolamine enhances its own absorption, and the pronounced difference between the species was not unexpected. The percent of dose absorbed in each species increased with increasing dose, but in rats, the increase was not statistically significant. Both species rapidly excreted the absorbed dose, primarily in urine. In rats, less than 1% of the dose was present in the tissue samples (except the dose site) 72 hours after treatment; the heart, kidney, liver, lung, and spleen contained elevated concentrations of radiolabel relative to blood.

After intravenous and dermal dosing in female rats and mice, triethanolamine was excreted, for the most part, unchanged in urine. Two additional polar peaks, each less than or equal to 5% of the total, were present in the urine. At least one of these polar peaks may have originated from impurities in the [^{14}C]-triethanolamine stock, which were better resolved from the test article peak during development of HPLC conditions for metabolite analysis.

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Table G1
Excretion of Radioactivity by Female Rats Following an Intravenous Dose of [^{14}C]-Triethanolamine[a]

Time (hours)	Urine	Feces	Total
6	38.2 ± 26.0		38.2 ± 26.0
24	90.5 ± 1.23	0.373 ± 0.106	90.9 ± 1.33
48	96.3 ± 1.38	0.580 ± 0.120	96.9 ± 1.50
72[b]	98.2 ± 1.85	0.630 ± 0.147	98.9 ± 1.99

[a] Samples were collected from four female rats per time point (feces not collected at 6 hours) after a 3 mg/kg intravenous dose; data are cumulative radioactivity excreted and presented as percent dose recovered (mean ± standard deviation).
[b] Includes urine from the bladder and final cage rinse

Table G2
Distribution of Radioactivity in Tissue of Female Rats Following an Intravenous Dose of [^{14}C]-Triethanolamine[a]

Tissue	ng-Eq[b] [^{14}C]-Triethanolamine/ g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	6.89 ± 0.508	0.857 ± 0.141	0.0167 ± 0.00101
Blood	8.13 ± 0.752	Unity	0.0146 ± 0.00145
Brain	21.3 ± 1.43	2.63 ± 0.103	0.00681 ± 0.000588
Heart	41.0 ± 2.97	5.06 ± 0.354	0.00447 ± 0.000231
Kidney	271 ± 16.5	33.6 ± 3.42	0.0597 ± 0.00515
Liver	257 ± 17.3	31.9 ± 5.11	0.272 ± 0.0189
Lung	109 ± 6.21	13.4 ± 0.747	0.0150 ± 0.00102
Muscle	26.9 ± 2.03	3.32 ± 0.215	0.447 ± 0.0332
Skin	15.1 ± 1.61	1.86 ± 0.158	0.0886 ± 0.00939
Spleen	67.8 ± 5.59	8.36 ± 0.710	0.00567 ± 0.0000251
Total in Tissues			0.930 ± 0.0384

[a] Samples were collected from four female rats at 72 hours after a 3 mg/kg intravenous dose; data are presented as mean ± standard deviation.
[b] Eq=Equivalents

TABLE G3
Excretion of Radioactivity by Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine[a]

Time (hours)	Urine	Feces	Total
68 mg/kg Dose Group			
6	0.171 ± 0.172		0.171 ± 0.172
24	1.33 ± 0.496	0.0080 ± 0.00446	1.34 ± 0.494
48	5.95 ± 2.71	0.0541 ± 0.0493	6.01 ± 2.75
72[b]	12.9 ± 5.84	0.247 ± 0.167	13.1 ± 5.70
276 mg/kg Dose Group			
6	0.135 ± 0.0793		0.135 ± 0.0793
24	3.03 ± 1.36	0.0148 ± 0.00738	3.04 ± 1.36
48	9.90 ± 2.52	0.0664 ± 0.0189	9.96 ± 2.53
72[b]	23.8 ± 7.82	0.142 ± 0.0471	23.9 ± 7.87

[a] Samples were collected from four (68 mg/kg) or three (276 mg/kg) female rats per time point (feces not collected at 6 hours); data are cumulative radioactivity excreted and presented as percent dose recovered (mean ± standard deviation).

[b] Includes urine from the bladder and final cage rinse

Table G4
Distribution of Radioactivity in Tissue of Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine[a]

Tissue	ng-Eq[b] [^{14}C]-Triethanolamine/ g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
68 mg/kg Dose Group			
Adipose	136 ± 72.0	0.746 ± 0.150	0.0131 ± 0.00703
Blood	174 ± 82.2	Unity	0.0124 ± 0.00599
Brain	214 ± 94.9	1.30 ± 0.301	0.00265 ± 0.00107
Heart	682 ± 305	3.98 ± 0.327	0.00293 ± 0.00135
Kidney	4,890 ± 2,250	28.2 ± 2.05	0.0467 ± 0.0226
Liver	2,840 ± 1,280	16.9 ± 3.44	0.113 ± 0.0471
Lung	1,520 ± 695	8.83 ± 0.867	0.00773 ± 0.00360
Muscle	584 ± 280	3.34 ± 0.440	0.386 ± 0.187
Skin	341 ± 198	2.03 ± 0.707	0.0799 ± 0.0471
Spleen	919 ± 389	5.47 ± 0.658	0.00290 ± 0.00134
Total in Tissues			0.668 ± 0.308
276 mg/kg Dose Group			
Adipose	1,200 ± 539	0.713 ± 0.144	0.0282 ± 0.0126
Blood	1,700 ± 758	Unity	0.0298 ± 0.0142
Brain	1,480 ± 685	0.870 ± 0.144	0.00463 ± 0.00234
Heart	6,080 ± 2,740	3.57 ± 0.223	0.00682 ± 0.00341
Kidney	39,300 ± 20,600	22.4 ± 2.67	0.0949 ± 0.0543
Liver	19,000 ± 8,270	11.3 ± 1.42	0.206 ± 0.0998
Lung	12,800 ± 5,660	7.54 ± 0.569	0.0169 ± 0.00844
Muscle	5,060 ± 1,630	3.15 ± 0.566	0.820 ± 0.289
Skin	2,640 ± 832	1.64 ± 0.299	0.151 ± 0.0520
Spleen	7,970 ± 3,680	4.66 ± 0.336	0.00627 ± 0.00331
Total in Tissues			1.36 ± 0.531

a Samples were collected from four (68 mg/kg) or three (276 mg/kg) female rats at 72 hours; data are presented as mean ± standard deviation.
b Eq=Equivalents

Table G5
Distribution of Absorbed and Unabsorbed Radioactivity in Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine[a]

	68 mg/kg	276 mg/kg
Absorbed		
Tissues	0.668 ± 0.308	1.36 ± 0.531
Dose site	5.62 ± 2.32	3.12 ± 0.881
Feces	0.247 ± 0.167	0.142 ± 0.0471
Urine	12.9 ± 5.84	23.8 ± 7.82
Total	19.4 ± 5.43	28.4 ± 9.08
Unabsorbed		
Dosing appliance	6.35 ± 4.11	2.99 ± 2.01
Skin gauze	22.9 ± 4.04	10.2 ± 4.39
Skin wash	37.2 ± 9.13	41.4 ± 3.54
Total	66.5 ± 5.26	54.6 ± 6.96

[a] Samples were collected from four (68 mg/kg) or three (276 mg/kg) female rats; data are presented as percent dose recovered (mean ± standard deviation).

Table G6
Excretion of Radioactivity by Female Mice Following an Intravenous Dose of [^{14}C]-Triethanolamine[a]

Time (hours)	Urine	Feces	Total
6	6.76 ± 8.29		6.76 ± 8.29
24	26.0 ± 17.2	14.3 ± 7.56	40.3 ± 10.3
48	42.6 ± 22.8	23.7 ± 13.1	66.2 ± 14.6
72[b]	61.9 ± 14.6	27.6 ± 10.4	89.5 ± 4.62

a Samples were collected from four female mice per time point (feces not collected at 6 hours) after a 3 mg/kg intravenous dose; data are cumulative radioactivity excreted and presented as percent dose recovered (mean ± standard deviation).
b Includes urine from the bladder and final cage rinse

Table G7
Distribution of Radioactivity in Tissue of Female Mice Following an Intravenous Dose of [^{14}C]-Triethanolamine[a]

Tissue	ng-Eq[b] [^{14}C]-Triethanolamine/ g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	17.1 ± 2.7	4.65 ± 1.29	0.0384 ± 0.00623
Blood	3.79 ± 0.578	Unity	0.00631 ± 0.000932
Brain	15.0 ± 1.12	4.02 ± 0.490	0.00835 ± 0.00158
Heart	32.7 ± 1.01	8.77 ± 1.28	0.00587 ± 0.000527
Kidney	106 ± 11.4	28.2 ± 3.75	0.0489 ± 0.00467
Liver	215 ± 33.8	57.7 ± 13.5	0.305 ± 0.0484
Lung	68.4 ± 5.45	18.2 ± 1.94	0.0123 ± 0.00193
Muscle	14.4 ± 1.27	3.87 ± 0.720	0.221 ± 0.0145
Skin	12.1 ± 1.19	3.24 ± 0.627	0.0658 ± 0.00797
Spleen	48.4 ± 2.15	12.9 ± 1.54	0.00425 ± 0.000225
Total in Tissues			0.716 ± 0.0685

a Samples were collected from four female mice 72 hours after a 3 mg/kg intravenous dose; data are presented as mean ± standard deviation.
b Eq=Equivalents

Table G8
Excretion of Radioactivity by Female Mice Following Dermal Administration of [^{14}C]-Triethanolamine[a]

Time (hours)	Urine	Feces	Total
79 mg/kg Dose Group			
6	3.04 ± 4.84		3.04 ± 4.84
24	22.5 ± 8.28	5.03 ± 3.09	27.5 ± 6.52
48	39.7 ± 4.96	7.07 ± 4.65	46.8 ± 7.28
72[b]	48.2 ± 5.09	7.8 ± 4.73	56.0 ± 8.05
1,120 mg/kg Dose Group			
6	0.000105 ± 0.00009		0.000105 ± 0.00009
24	39.7 ± 21.5	8.75 ± 6.02	48.4 ± 20.5
48	57.1 ± 18.1	11.8 ± 7.05	68.9 ± 13.1
72[b]	67.7 ± 14.9	13.0 ± 7.60	80.7 ± 7.96

[a] Samples were collected from four (79 mg/kg) or three (1,120 mg/kg) female mice per time point (feces not collected at 6 hours); data are cumulative radioactivity excreted and presented as percent dose recovered (mean ± standard deviation).
[b] Includes urine from the bladder and final cage rinse

Table G9
Distribution of Absorbed and Unabsorbed Radioactivity in Female Mice Following Dermal Administration of [^{14}C]-Triethanolamine[a]

	79 mg/kg	1,120 mg/kg
Absorbed		
Blood	0.00590 ± 0.00144	0.00627 ± 0.000412
Dose site	1.35 ± 0.317	0.576 ± 0.118
Feces	7.80 ± 4.73	13.0 ± 7.60
Urine	48.2 ± 5.09	67.7 ± 14.9
Total	57.3 ± 8.34	81.3 ± 8.02
Unabsorbed		
Dosing appliance	0.481 ± 0.301	1.68 ± 2.02
Skin gauze	2.30 ± 2.00	0.824 ± 0.737
Skin wash	11.8 ± 4.65	4.24 ± 2.13
Total	14.6 ± 2.84	6.75 ± 3.41

[a] Samples were collected from four (79 mg/kg) or three (1,120 mg/kg) female mice; data are presented as percent dose recovered (mean ± standard deviation).

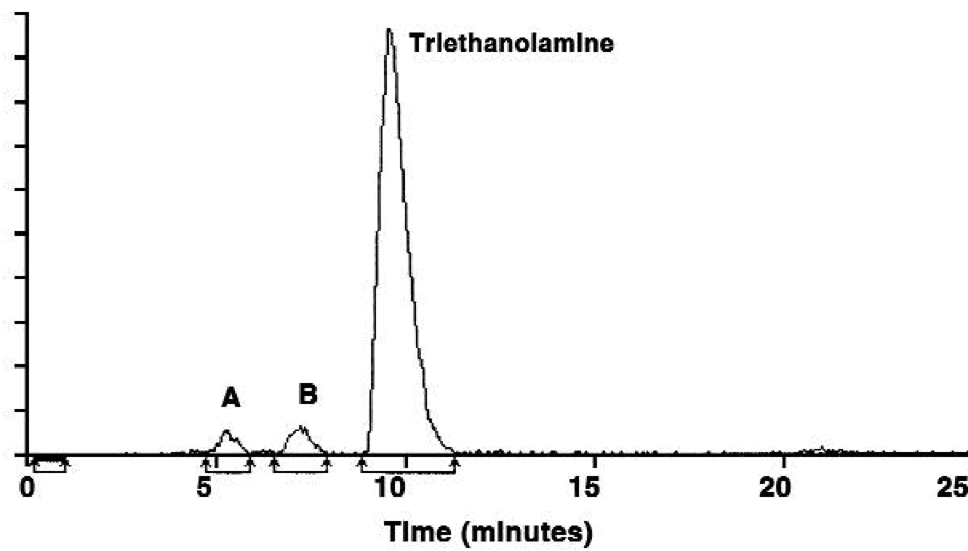

FIGURE G1
Radiochromatogram of Urine from Female Rats Following Dermal Administration of [^{14}C]-Triethanolamine
(urine collected 48 to 72 hours after dosing)

National Toxicology Program Technical Reports

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Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
2-Amino-4-Nitrophenol	339
2-Amino-5-Nitrophenol	334
11-Aminoundecanoic Acid	216
dl-Amphetamine Sulfate	387
Ampicillin Trihydrate	318
Asbestos, Amosite (Hamsters)	249
Asbestos, Amosite (Rats)	279
Asbestos, Chrysotile (Hamsters)	246
Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
Chlorinated Trisodium Phosphate	294
2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477

Chemical	TR No.
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
trans-Cinnamaldehyde	514
Citral	505
Cobalt Sulfate Heptahydrate	471
Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
Comparative Initiation/Promotion Studies (Mouse Skin)	441
Corn Oil, Safflower Oil, and Tricaprylin	426
Coumarin	422
CS2	377
Cytembena	207
D&C Red No. 9	225
D&C Yellow No. 11	463
Decabromodiphenyl Oxide	309
Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4´-Diamino-2,2´-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p´-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3´-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3´-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Elmiron®	512
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380
1,2-Epoxybutane	329

Chemical	TR No.
Erythromycin Stearate	338
Ethyl Acrylate	259
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
Eugenol	223
FD&C Yellow No. 6	208
Fumonisin B_1	496
Furan	402
Furfural	382
Furfuryl Alcohol	482
Furosemide	356
Gallium Arsenide	492
Geranyl Acetate	252
Glutaraldehyde	490
Glycidol	374
Guar Gum	229
Gum Arabic	227
HC Blue 1	271
HC Blue 2	293
HC Red 3	281
HC Yellow 4	419
Hexachlorocyclopentadiene	437
Hexachloroethane	361
2,4-Hexadienal	509
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
Indium Phosphide	499
Iodinated Glycerol	340
Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
Isophorone	291
Isoprene	486
Lauric Acid Diethanolamine Condensate	480
d-Limonene	347
Locust Bean Gum	221
60-Hz Magnetic Fields	488
Magnetic Field Promotion	489
Malonaldehyde, Sodium Salt	331
Manganese Sulfate Monohydrate	428
D-Mannitol	236
Marine Diesel Fuel and JP-5 Navy Fuel	310
Melamine	245
2-Mercaptobenzothiazole	332
Mercuric Chloride	408
Methacrylonitrile	497
8-Methoxypsoralen	359
α-Methylbenzyl Alcohol	369
Methyl Bromide	385
Methyl Carbamate	328
Methyldopa Sesquihydrate	348
Methylene Chloride	306
4,4´-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454

Chemical	TR No.
Nickel Subsulfide	453
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
p-Nitrophenol	417
o-Nitrotoluene	504
p-Nitrotoluene	498
Ochratoxin A	358
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
Propylene Glycol Mono-*t*-butyl Ether	515
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Riddelliine	508
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435
Titanocene Dichloride	399

Chemical	TR No.
Toluene	371
2,4- & 2,6-Toluene Diisocyanate	251
Triamterene	420
Tribromomethane	350
Trichloroethylene	243
Trichloroethylene	273
1,2,3-Trichloropropane	384
Tricresyl Phosphate	433
Triethanolamine	449
Triethanolamine	518
Tris(2-Chloroethyl) Phosphate	391
Tris(2-Ethylhexyl) Phosphate	274
Turmeric Oleoresin (Curcumin)	427
Vanadium Pentoxide	507
4-Vinylcyclohexene	303
4-Vinyl-1-Cyclohexene Diepoxide	362
Vinylidene Chloride	228
Vinyl Toluene	375
Xylenes (Mixed)	327
2,6-Xylidine	278
Zearalenone	235
Ziram	238

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