NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

DIETHANOLAMINE

(CAS NO. 111-42-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

July 1999

NTP TR 478

NIH Publication No. 99-3968

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.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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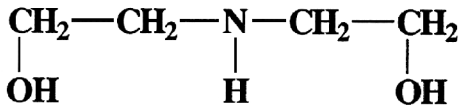
ABSTRACT



DIETHANOLAMINE

CAS No. 111-42-2

Chemical Formula: C H NO Molecular Weight: 105.14 4 11 2

Synonyms: Bis-2-hydroxyethylamine; DEA; diethylolamine; 2,2'-dihydroxydiethylamine; diolamine; 2,2'-iminobisethanol; iminodiethanol; 2,2'-iminodiethanol

Diethanolamine is widely used in the preparation of diethanolamides and diethanolamine salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. Diethanolamine is also used in textile pro-cessing, in industrial gas purification to remove acid gases, as an anticorrosion agent in metalworking fluids, and in preparations of agricultural chemicals. Aqueous diethanolamine solutions are used as solvents for numerous drugs that are administered intravenously. Diethanolamine was selected for evaluation because its large-scale production and pattern of use indicate the potential for widespread human exposure. Male and female F344/N rats and B6C3F_1 mice received dermal applications of diethanolamine in 95% ethanol for 2 years. Genetic toxicology studies were performed in *Salmonella typhimurium*, L5178Y were performed in Salmonella typhimurium, L5178Y ovary cells, and B6C3F1 mouse peripheral blood erythrocytes.

RATS

Groups of 50 male rats were administered 0, 16, 32, or 64 mg diethanolamine/kg body weight in ethanol dermally for 2 years. Groups of 50 female rats were administered 0, 8, 16, or 32 mg/kg in ethanol dermally for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of vehicle control and dosed male and female rats was similar. Mean body weights of 64 mg/kg males were less than those of the vehicle controls beginning week 8, and mean body weights of females were generally similar to those of the vehicle control group. The only clinical finding attributed to diethanolamine administration was irritation of the skin at the site of application.

Pathology Findings

Minimal to mild nonneoplastic lesions occurred at the site of application in the epidermis of dosed male and female rats. The incidence of acanthosis in 64 mg/kg males, the incidences of hyperkeratosis in 32 and 64 mg/kg males and in all dosed female groups, and the incidences of exudate in 64 mg/kg males and in all dosed female groups were greater than those in the controls.

The incidences and severities of nephropathy were significantly increased in dosed female rats compared to the vehicle controls.

MICE

Groups of 50 male and 50 female mice were administered 0, 40, 80, or 160 mg diethanolamine/kg body weight in ethanol dermally for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of dosed male groups was similar to that of the vehicle control group; survival of dosed female groups was significantly less than that of the vehicle control group. Mean body weights of 80 and 160 mg/kg males were less than those of the vehicle controls after weeks 88 and 77, respectively. Mean body weights of dosed groups of females were generally less than those of the vehicle controls during the second year of the study.

Pathology Findings

In male mice, the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in all dosed groups and of hepatocellular carcinoma and hepatoblastoma in 80 and 160 mg/kg males were significantly increased compared to the vehicle controls. The incidences of hepatocellular neoplasms were significantly greater in dosed groups of female mice than in the vehicle control group. The incidences of hepatocellular neoplasms in all dosed groups of males and females exceeded the historical control ranges. Nonneoplastic hepatocyte changes were seen only in dosed male and female mice. Changes consisted of cytoplasmic alteration and syncytial alteration.

The incidences of renal tubule adenoma in males occurred with a positive trend; however, the incidences of carcinoma and hyperplasia did not follow this pattern. An extended evaluation of kidney step sections revealed additional adenomas and hyperplasias in all dosed groups. The combined analysis of single and step sections indicated a dose-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma or carcinoma (combined), and an increase in the incidences of renal tubule adenoma in male mice.

Incidences of thyroid gland follicular cell hyperplasia were increased in dosed male and female mice compared to vehicle controls.

Hyperkeratosis, acanthosis, and exudate were treatment-related changes in the skin at the site of application. The incidences of hyperkeratosis were significantly greater than those in the vehicle control groups in all dosed groups except 40 mg/kg females.

GENETIC TOXICOLOGY

Diethanolamine was not mutagenic in any of four strains of *Salmonella typhimurium*, in the presence or absence of S9 metabolic activation enzymes. No induction of trifluorothymidine resistance was observed in L5178Y mouse lymphoma cells treated with diethanolamine with or without S9. Diethanolamine did not induce significant sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9. Peripheral blood samples collected from male and female mice exposed to 80 to 1,250 mg/kg diethanolamine dermally for 13 weeks showed no increase in micronucleated normochromatic erythrocytes.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diethanolamine in male F344/N rats administered 16, 32, or 64 mg/kg diethanolamine or in female F344/N rats administered 8, 16, or 32 mg/kg. There was *clear evidence of carcinogenic activity** of diethanolamine in male and female B6C3F_1 mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males.

Dermal administration of diethanolamine to rats was associated with increased incidences of acanthosis (males only), hyperkeratosis, and exudate of the skin and increased incidences and severities of nephropathy in females. Dermal administration of diethanolamine to mice was associated with increased incidences of cytoplasmic alteration (males only) and syncytial alteration of the liver, renal tubule hyperplasia (males only), thyroid gland follicular cell hyperplasia, and hyperkeratosis of the skin.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses in ethanol by dermal application	0, 16, 32, or 64 mg/kg	0, 8, 16, or 32 mg/kg	0, 40, 80, or 160 mg/kg	0, 40, 80, or 160 mg/kg
Body weights	64 mg/kg groups generally less than vehicle control groups	Dosed groups generally similar to vehicle control group	80 and 160 mg/kg groups less than vehicle control group	Dosed groups generally less than vehicle control group
Survival rates	14/50, 10/50, 21/50, 22/50	25/50, 29/50, 29/50, 24/50	40/50, 43/50, 34/50, 30/50	44/50, 33/50, 33/50, 23/50
Nonneoplastic effects	Skin: acanthosis (0/50, 2/50, 4/50, 10/50); hyperkeratosis (0/50, 3/50, 5/50, 11/50); exudate (0/50, 3/50, 2/50, 7/50)	Skin: hyperkeratosis (3/50, 13/50, 23/50, 23/50); exudate (1/50, 7/50, 7/50, 7/50) Kidney: nephropathy (40/50, 47/50, 48/50, 48/50); severity (1.2, 1.5, 1.9, 2.7)	Liver: cytoplasmic alteration (1/50, 17/50, 17/50, 12/50); syncytial alteration (0/50, 28/50, 38/50, 23/50) Kidney: renal tubule hyperplasia (standard and extended evaluation combined (3/50, 7/50, 7/50, 10/50) Thyroid gland: follicular cell hyperplasia (18/50, 22/49, 30/50, 42/50) Skin: hyperkeratosis (0/50, 13/50, 10/50, 17/50)	Liver: syncytial alteration (0/50, 2/50, 17/50, 18/50) Thyroid gland: follicular cell hyperplasia (18/50, 28/49, 32/50, 39/50) Skin: hyperkeratosis (1/50, 3/50, 8/50, 16/50)
Neoplastic effects	None	None	Liver: hepatocellular adenoma (31/50, 42/50, 49/50, 45/50); hepatocellular carcinoma (12/50, 17/50, 33/50, 34/50); hepatoblastoma (0/50, 2/50, 8/50, 5/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (39/50, 47/50, 50/50, 49/50) Kidney: adenoma (standard evaluation - 1/50, 4/50, 6/50, 6/50; standard and extended evaluation combined - 1/50, 6/50, 8/50, 7/50); adenoma or carcinoma (combined) (standard evaluation -3/50, 5/50, 6/50, 8/50; standard and extended evaluation combined - 3/50, 7/50, 8/50, 9/50)	Liver: hepatocellular adenoma (32/50, 50/50, 48/50, 48/50); hepatocellular carcinoma (5/50, 19/50, 38/50, 42/50); hepatocellular adenoma or carcinoma (33/50, 50/50, 50/50, 50/50)

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	No evidence	No evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537			
Mouse lymphoma gene mutations:	Negative			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative			
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.

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 diethanolamine on 9 December 1997 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 9 December 1997, the draft Technical Report on the toxicology and carcinogenicity studies of diethanolamine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of diethanolamine by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male and female F344/N rats and *clear evidence of carcinogenic activity* in male and female $B6C3F_1$ mice.

Dr. Goldsworthy, a principal reviewer, agreed with the proposed conclusions. He said that, because a majority of neoplasm responses observed in the companion studies of the fatty acid/diethanolamine condensates were concluded to result from the presence of free diethanolamine, some of his comments would also pertain to the condensates. Dr. Goldsworthy commented that the report should address if and how the distribution and metabolism of diethanolamine would be altered at various test concentrations and by the potential interactions with the different condensates. He said that, besides trying to link diethanolamine concentrations with neoplastic responses, it would be useful to chart comparative toxicities between the condensates and diethanolamine concentrations, as well as the potential for nitrosamine formation. Dr. Goldsworthy asked about the significance of the hepatoblastomas in treated male mice. Dr. J.R. Hailey, NIEHS, said that hepatoblastoma is a neoplasm with a fairly distinct morphology composed of primitive-appearing cells and appears to be part of the spectrum of the progression of liver neoplasms in the mouse; as such, with the higher background rate of liver neoplasms in mice, there is a concomitant increase in the incidence of hepatoblastoma.

Dr. Bailer, the second principal reviewer, agreed in principle with the proposed conclusions. He said the conclusions should be modified to note the significant negative trend in female rat mammary gland fibroadenomas and the increased survival experienced by rats administered diethanolamine. Dr. J.K. Haseman, NIEHS, said that a decrease in the incidence of mammary gland neoplasms is often associated with reduced body weight, although not in this case; therefore, more discussion might be merited. Dr. Bailer commented that the high liver neoplasm rates in control mice emphasize the importance of the concurrent controls in these studies, especially since the historical control database is so small for dermal studies using an ethanol vehicle.

Dr. Chatman, the third principal reviewer, did not agree with the conclusions for mice. She stated that diethanolamine is not a mutagen and is not metabolized to a reactive intermediate but can be converted to a carcinogenic nitrosamine. She felt that the potential for N-nitrosodiethanolamine formation should have been evaluated. Dr. Chatman referred to a letter received by the reviewers from the Alkanolamines Panel of the Chemical Manufacturers Association (CMA), which reported that rodent feed during some weeks of the studies was contaminated with high bacterial counts. She thought this could have enhanced N-nitroso-diethanolamine formation. Dr. Irwin responded that published studies with N-nitrosodiethanolamine given in drinking water show it to be a potent liver carcinogen in F344/N rats but a noncarcinogen in $B6C3F_1$ mice.

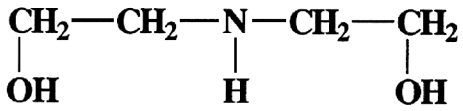
There were questions about the possible impact of *Helicobacter hepaticus* on the incidence of liver neoplasms in mice. Dr. Hailey said that in frozen tissues from about 20 animals, 10 males and 10 females, polymerase chain reaction analysis for *H. hepaticus* was negative. Dr. Goldsworthy asked for comment on the impact of increased liver neoplasm rates in control mice relative to interpretation of bioassay results. Dr. Hailey replied that, in view of higher background incidence, other components have to be assessed, especially progression to a malignant state and increases in numbers or multiplicity; both were

dramatically increased in these studies. Dr. Hecht agreed that formation of nitrosamines was not likely, but he was disappointed with the lack of detail in the analytical methods description so that contamination of diethanolamine with N-nitroso-diethanolamine could not be ruled out. Dr. Irwin said he would increase the detail in the analytical methods. Dr. G.N. Rao, NIEHS, stated that standards for the NIH-07 diet used since 1984 are much more stringent than those of most commercially available diets with regard to allowable bacterial counts.

Dr. W. Stott, Dow Chemical Company, representing the Alkanolamines Panel of the CMA, said that their major concerns with the study were questions about technical aspects of the bioassay and the inconsistency between the genotoxicity and carcinogenicity findings. Among technical questions which he thought should have been better discussed in the report were the choice of a dermal rather than an oral route of administration, the use of an ethanol vehicle, which has potential promo-tional/carcinogenic effects in itself, the potential for nitrosamine formation *in vivo*, and high liver neoplasm incidence in control mice. Dr. Stott reported that the Alkanolamines Panel plans to conduct mechanistic studies to help understand the NTP mouse bioassay results and their relevance to humans.

Dr. Goldsworthy moved that the Technical Report on diethanolamine be accepted with the revisions discussed and the conclusions as written for male and female rats, *no evidence of carcinogenic activity*, and for male and female mice, *clear evidence of carcinogenic activity*. Dr. Bailer seconded the motion, which was accepted with six yes votes to one no vote (Dr. Chatman) and one abstention (Dr. Bus).

INTRODUCTION



DIETHANOLAMINE

CAS No. 111-42-2

Chemical Formula: C H NO Molecular Weight: 105.14 4 11 2

Synonyms: Bis-2-hydroxyethylamine; DEA; diethylolamine; 2,2'-dihydroxydiethylamine; diolamine; 2,2'-iminobisethanol; iminodiethanol; 2,2'-iminodiethanol

CHEMICAL AND PHYSICAL PROPERTIES

Diethanolamine is a secondary amine in which two molecules of ethanol are linked through their beta carbons to a common nitrogen. It is a colorless or faintly colored crystalline solid at room temperature but melts at 28° C. It is soluble in water, alcohol, ethanol, and benzene but insoluble in most other organic solvents. In aqueous solutions, the pK of the a secondary amine is 8.88 at 25° C (Merck Index, 1989; *Hazardous Chemicals Desk Reference*, 1993).

PRODUCTION, USE, AND HUMAN EXPOSURE

Diethanolamine is produced by reacting two moles ethylene oxide with one mole of ammonia. In most production facilities, ethylene oxide and ammonia are are reacted in a bath process that yields a crude mixture of ethanolamine, diethanolamine, and triethanolamine. The mixture is then distilled to separate and purify the individual compounds (*Kirk-Othmer,* 1985). Diethanolamine is a high-production chemical; the worldwide production capacity for ethanolamines was estimated at 300,000 metric tons in 1992. United States production of ethanolamines was 447,727 metric tons in 1995; diethanolamine represented approximately one third of the total production (SRI, 1995).

There is potentially widespread occupational and consumer exposure to diethanolamine. It is widely used in the preparation of diethanolamides and diethanolamine salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. Diethanolamine is also used in textile processing, in industrial gas purification to remove acid gases, as an anticorrosion agent of in metalworking fluids, and in preparations of agricultural chemicals. Aqueous diethanolamine solutions used as solvents for numerous drugs administered intravenously (*Merck Index,* 1989; *Hazardous Chemicals Desk Reference*, 1993). A review by Knaak *et al.* (1997) contains an excellent summary of additional uses of diethanolamine. The National Occupational Exposure Survey estimated that, during 1981 through 1983, 828,450 workers were occupationally exposed to diethanolamine (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Diethanolamine produces toxic responses after oral, dermal, or inhalation exposure; however, dermal exposure is the most important route of both occupational and consumer exposure. The percutaneous absorption of diethanolamine has been evaluated in F344/N rats and $B6C3F_1$ mice (NTP, 1991). Forty-eight hours after application of 2.1, 7.6, or 27.5 mg ^{14}C-labeled diethanolamine per kg body weight in 95% ethanol (total volume applied 25 μL) on a 2 cm^2 area of the intrascapular region of male F344/N rats, 2.9%, 10.5%, or 16.2%, respectively, of the applied dose had been absorbed. Based on diethanolamine recovered from tissues and excreta, 1.2%, 4.3%, or 4.5% was present in skin (washed to remove unabsorbed material) at the site of application. Male $B6C3F_1$ mice received a single dose of 81.1 mg/kg in 15 μL on a 1 cm^2 area of the intrascapular region; 48 hours after application, 58.1% of the dose was recovered in tissues or excreta of which 2.2% was present in skin at the site of application. In a separate study by Waechter, reported in Knaak *et al.* (1997), 1,500 mg/kg ^{14}C-labeled diethanolamine was applied to the intrascapular region of male F344 rats. Excluding skin from the site of application, 1.4% of the applied dose had been absorbed after 48 hours. Knaak *et al.* (1997) plotted absorption rates ($\mu g/cm^2$ per hour) as a function of applied dose determined from the NTP (1991) data and that determined from the study by Waechter and found that the rate of percutaneous absorption of diethanolamine increases linearly with the applied dose.

Diethanolamine was eliminated very slowly in the urine and feces of rats and mice following single intravenous, oral, or dermal administrations (Table 1; NTP 1991). Only trace amounts of radioactivity were detected in volatile metabolites (Matthews *et al.*, 1995).

TABLE 1
Elimination of ^{14}C-Diethanolamine in F344/N Rats and $B6C3F_1$ Mice[a]

Dose	Collection Period (hours)	Percentage[b] of Dose in:	
		Urine	Feces
Rats			
7.5 mg/kg intravenous	24	16.5 ± 1.9	0.35 ± 0.02
	48	28.3 ± 2.5	0.60 ± 0.03
7.9 mg/kg oral	24	9.0 ± 2.5	1.60 ± 0.20
	48	22.00 ± 1.80	2.42 ± 0.33
7.6 mg/kg dermal	48	16.2[c]	1.9[c]
Mice			
14.9 mg/kg intravenous	24	11.5 ± 7.0	1.6 ± 0.36
	48	25.5 ± 5.0	2.98 ± 0.86
81.1 mg/kg dermal	48	28.3[c]	4.4[c]

[a] These data are presented by NTP, 1991.
[b] Mean ± standard error
[c] Calculated from dermal absorption data

With repeated oral dosing, diethanolamine accumulated in tissues and eventually reached a steady state within 4 to 8 weeks (NTP, 1991). In F344/N rats administered ^{14}C-diethanolamine at daily oral doses of 7 mg/kg for 14 days followed by a 14-day washout period, elimination of the radiolabel in the urine and feces was consistent with an approximate half-life of 1 week (NTP, 1991).

Administration of ^{14}C-diethanolamine to F344/N rats by the intravenous, oral, or dermal routes led to similar tissue distribution; the greatest number of diethanolamine equivalents present 48 hours after a single dose were found in the liver and kidney (NTP, 1991; Matthews *et al.*, 1995). For the oral and dermal routes, lesser amounts of diethanolamine were also found in the brain and heart; with the intravenous route, lesser amounts were found in the spleen and lung. Extraction with phosphate-buffered saline and chloroform/methanol indicated that 87% to 89% of the radioactivity in the liver and brain partitioned into the aqueous phase, whereas 6% to 9% was removed by the organic extraction. Identification of the radioactive species present revealed that 70% to 80% of the radioactivity present in aqueous extracts of liver and brain was the parent compound, diethanolamine. Two minor metabolites, N-methyl-diethanolamine and N,N-dimethyl-diethanolamine, and several phosphorylated forms accounted for the remainder of the water-soluble radioactivity found in the liver. Diethanolamine-phosphate accounted for 95% of the phosphorylated metabolites present, and N,N-dimethyldiethanolamine-phosphate and N-methyldiethanolaminephosphate each constituted 2% of the phosphorylated metabolites extracted.

The chloroform/methanol extracts of liver contained two radioactive components associated with the phosphatidylethanolamine and phosphatidylcholine fractions. Upon incubation of the phosphatidylethanolamine fraction with phospholipase D, the radiolabel was liberated quantitatively as diethanolamine, whereas phospholipase D treatment of the phosphatidylcholine fraction yielded N-methyldiethanolamine (15%) and N,N-dimethyldiethanolamine (85%). Incubation of chloroform/methanol extracts from brain tissue with phospholipase D yielded only radioactive diethanolamine. Further analysis revealed that approximately 30% of diethanolamine-containing phospholipids in liver were ceramides and 70% were phosphoglycerides. These results indicated that diethanolamine was incorporated into phospholipid headgroups by the same pathway that led to the incorporation of ethanolamine, the natural substrate for these reactions (NTP, 1991; Matthews *et al.*, 1995).

Analysis of aqueous and organic extracts from the livers and brains of rats receiving daily oral doses of ^{14}C-diethanolamine for 8 weeks revealed that 97% of the radioactivity in the liver and 77% of the radioactivity in the brain were present in the aqueous extract and represented primarily free diethanolamine. Analysis of the organic extract from liver indicated that all radioactivity was associated with the phosphatidylcholine fraction and was present as N,N-dimethyldiethanolamine headgroups in ceramide derivatives. Analysis of the organic extract from brain revealed that all radioactivity was associated with the phosphatidylethanolamine fraction and that approximately 65% was present in ceramide derivatives (Matthews *et al.,* 1995). In human liver slices incubated with ^{14}C-diethanolamine, diethanolamine was readily incorporated into ceramide containing phospholipids in the form of phosphodiethanolamine headgroups, which were then slowly methylated (Matthews *et al.,* 1995).

TOXICITY

Experimental Animals

The acute toxicity of diethanolamine is summarized in Table 2.

The prechronic toxicology of diethanolamine has been evaluated in rats and mice in 13-week studies in which diethanolamine was administered by dermal application or in drinking water (Melnick *et al.,* 1994a,b). In the dermal study, solutions containing 0, 32, 63, 125, 250 or 500 mg/kg diethanolamine in 95% ethanol were applied to the shaved interscapular region of groups of 10 male and 10 female F344 rats 5 days per week for 13 weeks. One male rat and two female rats receiving 500 mg/kg died before the end of the study, and mean body weights of males that received 250 or 500 mg/kg and of females that received 125, 250, or 500 mg/kg were significantly less than those of the vehicle controls during the study.

TABLE 2
Acute Toxicity of Diethanolamine

Route	Species	LD_{50} (mg/kg)	Reference
Oral	rat	710; 1,820	HSDB, 1997
	rat, male	1,700 — 2,800	Knaak *et al.,* 1997
	rat, female	700 — 1,700	Knaak *et al.,* 1997
	mouse	3,300	Knaak *et al.,* 1997
Intraperitoneal	mouse	2,300	HSDB, 1997
Subcutaneous	mouse	3,553	HSDB, 1997
Dermal	rabbit	8,100 — 12,200	Knaak *et al.,* 1997

Hematology evaluations conducted at study termination revealed the presence of a normochromic, microcytic anemia in males and females, characterized by dose-dependent decreases in erythrocyte count, hemoglobin concentration, hematocrit, mean cell volume, mean cell hemoglobin, and reticulocyte counts in females but not males. In males, decreases were observed primarily at doses of 125 mg/kg and greater, whereas decreases were observed in all dosed groups of females.

The histopathologic lesions associated with dermal administration of diethanolamine to rats are shown in Table 3. Skin was the major site affected in dosed males, with hyperkeratosis and acanthosis apparent in groups that received 63 mg/kg and above. Skin was also affected in dosed females; however, incidences of nephropathy were increased in all dosed groups except the 500 mg/kg group, incidences of mineralization were increased in all dosed groups, and renal tubule epithelial necrosis was present in the 250 and 500 mg/kg female groups. Demyelination of the medulla occurred in males receiving 500 mg/kg and females receiving 250 or 500 mg/kg.

In the drinking water study, groups of 10 male F344/N rats received drinking water containing 0, 320, 630, 1,250, 2,500, or 5,000 ppm diethanolamine, and groups of 10 female F344/N rats received drinking water containing 0, 160, 320, 630, 1,250, or 2,500 ppm diethanolamine continuously for 13 weeks. Actual estimated daily intakes were 0, 25, 48, 97, 202, or 436 mg/kg (males) and 0, 14, 32, 57, 124, or 242 mg/kg (females). Two males exposed to 5,000 ppm died before the end of the study. Mean body weights of males exposed to 630 ppm or greater and females exposed to 320 ppm or greater were less than those of the controls during the study. Hematology evaluations conducted at study termination indicated the presence of a normochromic, microcytic anemia similar to that observed in the dermal study. Histopathologic lesions associated with exposure to diethanolamine included exposure-related increases in the severities of nephropathy and incidences of renal tubule mineralization in males and females, demyelination of the brain and spinal cord in females exposed to 1,250 or 2,500 ppm and males exposed 2,500 or 5,000 ppm, and degeneration of the seminiferous tubules in males exposed to 2,500 ppm or greater.

TABLE 3
Incidence of Selected Nonneoplastic Lesions in Rats in the 13-Week Dermal Study of Diethanolamine[a]

	Vehicle Control		32 mg/kg		63 mg/kg		125 mg/kg		250 mg/kg		500 mg/kg	
Male												
Kidney[b]	10		10		10		10		10		10	
Nephropathy[c]	9	(1.0)[d]	6	(1.0)	5	(1.0)	6	(1.0)	4	(1.0)	5	(1.0)
Renal Tubule Epithelial Necrosis	0		0		0		0		0		0	
Renal Tubule Mineralization	0		0		0		0		0		9**	(1.9)
Brain, Medulla	10		10		10		10		10		10	
Demyelination	0		0		0		0		0		10**	(1.0)
Skin	10		10		10		10		10		10	
Ulcer	0		0		0		0		3	(1.3)	10**	(2.6)
Chronic Active Inflammation	0		0		0		0		3	(1.3)	10**	(1.7)
Acanthosis	0		0		3	(1.0)	6**	(1.0)	6**	(1.5)	10**	(2.2)
Hyperkeratosis	0		0		5*	(1.0)	10**	(1.1)	10**	(1.4)	10**	(1.9)
Female												
Kidney	10		10		10		10		10		10	
Nephropathy	3	(1.0)	9**	(1.3)	10**	(1.4)	10**	(1.7)	7*	(1.1)	4	(1.0)
Renal Tubule Epithelial Necrosis	0		0		0		0		2	(1.0)	10**	(1.0)
Renal Tubule Mineralization	4	(1.0)	9*	(1.0)	10**	(1.6)	10**	(1.9)	10**	(1.1)	10**	(1.0)
Brain, Medulla	10		10		10		10		10		10	
Demyelination	0		0		0		0		7**	(1.0)	10**	(1.0)
Skin	10		10		10		10		10		10	
Ulcer	0		0		0		1	(1.0)	7**	(1.9)	10**	(3.4)
Chronic Active Inflammation	0		0		0		3	(1.0)	7**	(1.6)	10**	(2.5)
Acanthosis	0		0		1	(1.0)	6**	(1.2)	7**	(2.0)	10**	(2.6)
Hyperkeratosis	0		5*	(1.0)	6**	(1.0)	9**	(1.2)	10**	(1.7)	10**	(2.1)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] These data are presented by Melnick *et al.*, 1994a.
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

In companion studies (Melnick *et al.*, 1994b), groups of 10 male and 10 female B6C3F$_1$ mice received doses of 0, 80, 160, 320, 630, or 1,250 mg/kg by dermal application to the shaved interscapular region 5 days per week for 13 weeks. Two males and four females administered 1,250 mg/kg died before the end of the study. Final mean body weights of males receiving 1,250 mg/kg were slightly less than that of the vehicle controls, but final mean body weights of other dosed groups were similar to those of the

vehicle controls. Liver and kidney weights were significantly increased compared to the vehicle controls in groups of males administered 160 mg/kg or greater and females receiving 80 mg/kg or greater. Serum alanine aminotransferase and sorbitol dehydrogenase activities were significantly increased in males that received 630 or 1,250 mg/kg, and serum alanine aminotransferase activity was increased in females that received 1,250 mg/kg.

Histopathologic lesions associated with dermal administration of diethanolamine to mice are shown in Table 4 (Melnick *et al.*, 1994b). Acanthosis occurred at the site of application in all animals administered diethanolamine but was not observed in the vehicle controls. Cytologic alteration of the liver was observed in all groups of male mice administered diethanolamine and in females receiving 160 mg/kg or greater. Hepatocellular necrosis was also present in several dosed groups of males, especially groups receiving 320 mg/kg or greater. Renal tubule necrosis and cardiac degeneration were observed in males and females receiving 1,250 mg/kg.

In the mouse drinking water study, groups of 10 male and 10 female $B6C3F_1$ mice were given drinking water containing 0, 630, 1,250, 2,500, 5,000 or 10,000 ppm diethanolamine. Actual estimated daily intake was 0, 104, 178, 422, 807, or 1,674 mg/kg (males) and 0, 142, 347, 884, 1,154, or 1,128 mg/kg (females). All groups exposed to 5,000 or 10,000 ppm died before the end of the study; mean body weights of males and females exposed to 2,500 ppm were less than those of the controls during the study. Liver weights were significantly increased in groups of males and females exposed to 630, 1,250, or 2,500 ppm. Kidney weights were also increased in males exposed to 2,500 ppm. Histopathologic lesions observed in the drinking water study included exposure-related increases in the incidences and severities of cytologic alteration of the liver in males and females, the incidence of nephropathy in groups of males that survived to study termination, and cardiac degeneration in males and females exposed to 2,500 ppm or greater.

Humans

No references to human toxicity were found in a review of the current literature on diethanolamine.

CARCINOGENICITY

Experimental Animals

The carcinogenic potential of diethanolamine has not been previously evaluated; however, the carcinogenic potential of N-nitrosodiethanolamine has been examined in several studies. Lijinsky *et al.* (1980) administered N-nitrosodiethanolamine in drinking water at concentrations of 3,900, 7,800, 15,600, or 31,250 ppm to groups of 10 male and 10 female F344 rats, 5 days per week for 34 weeks. All exposed animals developed hepatocellular carcinomas, and the incidences of cholangiocarcinoma were increased in groups exposed to 7,800 ppm or greater. A number of studies (Preussmann *et al.*, 1981; Konishi *et al.*, 1987) demonstrated that N-nitrosodiethanolamine formed *in vivo* in rats coadministered diethanolamine and nitrite. Yamamoto *et al.* (1995) examined the ability of N-ni-trosodiethanolamine formed *in situ* to initiate hepatocytes *in vivo*. Groups of 11 male Wistar rats were exposed to feed containing 0.5% diethanolamine and drinking water containing 0.3% sodium nitrite. Control groups received either no exposure to diethanolamine, sodium nitrite only, or diethanolamine only. After 2 weeks, the animals underwent partial hepatectomy and were then maintained on the same diet for another week, after which they were exposed to diets containing 0.02% 2-acetylaminofluorene for 2 weeks, with a single injection of carbon tetrachloride administered between the first and second weeks. One week later the animals were killed and the number of γ-glutamyltranspeptidase-positive hepatic foci was determined to assay for initiation activity. The numbers of γ-glutamyltranspeptidase-positive foci per cm^2 in groups administered diethanolamine alone or nitrite alone were the same as in the control group. The number of positive foci per cm^2 was significantly increased in the group exposed to diethanolamine and nitrite, suggesting that N-nitrosodiethanolamine formed *in situ* could initiate rat liver.

Humans

No references to carcinogenicity in humans were found in a review of the current literature on diethanolamine.

TABLE 4
Incidence of Selected Nonneoplastic Lesions in Mice in the 13-Week Dermal Study of Diethanolamine[a]

	Vehicle Control	80 mg/kg	160 mg/kg	320 mg/kg	630 mg/kg	1,250 mg/kg
Male						
Liver[b]	10	10	10	10	10	10
Cytologic Alteration[c]	0	5* (1.0)[d]	10** (1.0)	10** (1.4)	10** (2.0)	10** (2.5)
Hepatocellular Necrosis	0	2 (1.0)	0	3 (1.3)	7** (1.1)	6** (2.0)
Kidney	10	0	0	0	10	10
Renal Tubule Epithelial Necrosis	0	0	0	0	0	4* (1.3)
Heart	10	0	0	0	10	10
Degeneration	0	0	0	0	0	1* (2.0)
Skin	10	10	10	10	10	10
Ulcer	0	0	0	0	2 (2.0)	10** (3.0)
Chronic Active Inflammation	0	0	0	0	5* (1.2)	10** (2.7)
Acanthosis	0	10** (1.0)	9** (1.0)	9** (1.1)	10** (2.6)	10** (2.9)
Hyperkeratosis	0	0	0	2 (1.5)	5* (1.8)	10** (2.0)
Female						
Liver	10	10	10	10	10	10
Cytologic Alteration	0	0	10** (1.0)	9** (1.1)	10** (1.3)	9** (1.3)
Kidney	10	0	0	0	10	10
Renal Tubule Epithelial Necrosis	0	0	0	0	0	1 (1.0)
Heart	10	0	10	0	10	10
Degeneration	0	0	0	0	0	8** (1.6)
Skin	10	10	10	10	10	10
Ulcer	0	0	0	0	1 (1.0)	9** (3.3)
Chronic Active Inflammation	0	0	0	1 (1.0)	1 (1.0)	9** (3.0)
Acanthosis	0	10** (1.0)	10** (1.0)	9** (1.0)	10** (1.3)	10** (2.9)
Hyperkeratosis	0	0	0	0	0	10** (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] These data are presented by Melnick *et al.*, 1994b.
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICITY

Diethanolamine has been tested for mutagenicity in several short-term tests, and in general, the data indicate little evidence for activity. No mutagenic activity was noted in bacterial assays (Haworth *et al.*, 1983; Dean *et al.*, 1985) or in the yeast, *Saccharomyces cerevisiae* (Dean *et al.*, 1985). Diethanolamine did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells (Inoue *et al.*, 1982; Sorsa *et al.*, 1988; Loveday *et al.*, 1989). In addition, no cell transformation occurred in cultured Chinese hamster ovary cells treated with diethanolamine *in vitro* (Inoue *et al.*, 1982). Positive results were reported in an *in vitro* assay for induction of DNA single-strand breaks in freshly isolated hepatocytes from rats, hamsters, and pigs (Pool *et al.*, 1990).

Triethanolamine, a structural analogue of diethanolamine, was studied in several genetic toxicity tests and was found to be negative in bacterial mutagenicity assays (Inoue *et al.*, 1982; Dean *et al.*, 1985; Mortelmans *et al.*, 1986) and in the *Drosophila melanogaster* sex-linked recessive lethal mutation assay (Yoon *et al.*, 1985). It did not induce gene conversion in *S. cereviseae* (Dean *et al.*, 1985) or DNA damage in *Escherichia coli* (Inoue *et al.*, 1982). No induction of sister chromatid exchanges was noted in cultured Chinese hamster ovary cells treated with triethanolamine (Galloway *et al.*, 1987), and tests for induction of chromosomal aberrations in cultured rat liver cells (Dean *et al.*, 1985) and cultured Chinese hamster ovary cells (Inoue *et al.*, 1982; Galloway *et al.*, 1987) also gave negative results.

STUDY RATIONALE

Diethanolamine was selected for evaluation because its large-scale production and pattern of use indicate the potential for widespread human exposure. In addition, the toxicity and carcinogenic potential associated with long-term exposure had not been examined. Based on the pattern of occupational and consumer exposure, dermal administration was considered the most appropriate route for the 2-year study.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Diethanolamine

Diethanolamine was obtained from Kodak Laboratory and Specialty Chemicals (Rochester, NY) in one lot (A16) which was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix F). Reports on analyses performed in support of the diethanolamine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless, viscous liquid, was identified as diethanolamine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and by boiling point and density. The purity of lot A16 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for diethanolamine. Karl Fischer water analysis indicated 0.10% ± 0.02% water. Functional group titration indicated a purity of 100.1% ± 0.7%. Analysis by thin-layer chromatography indicated a major spot and one trace impurity by one system and a major spot and two trace impurities by a second system. Gas chromatography by two systems indicated no impurities equal to or greater than 0.1% relative to the major peak. The overall purity of lot A16 was determined to be greater than 99%.

An accelerated stability study was performed by the analytical chemistry laboratory using gas chromatography. This study indicated that diethanolamine was stable as a bulk chemical for 2 weeks when protected from light and stored at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in sealed amber glass containers in a metal drum, at room temperature. Stability was monitored by the study laboratory using gas chromatography. No degradation of the bulk chemical was detected.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY). The purity was monitored by the study laboratory throughout the study by gas chromatography. United States Pharmacopeia ethanol reference standard samples were analyzed concomitantly. Purity of the bulk ethanol ranged from 98.7% to 101.3% that of the reference standard during the studies. No volatile impurities were detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by mixing diethanolamine with 95% ethanol to give the desired concentration (Table F1). The dose formulations were stored at room temperature, protected from light, in amber glass bottles for up to 28 days.

Stability studies of a 0.5 mg/mL formulation were performed by the analytical chemistry laboratory using gas chromatography. The formulation had only small losses of diethanolamine (<5%) when stored at room temperature, protected from light, for up to 28 days; it was stable for 3 hours when stored open to air and light.

Periodic analyses of the dose formulations of diethanolamine were conducted at the study laboratory using gas chromatography. Dose formulations were analyzed approximately every 9 weeks. All dose formulations and animal room samples for rats and mice were within 10% of the target concentrations.

2-YEAR STUDIES

Study Design

Groups of 50 male rats were administered dermal doses of 0, 16, 32, or 64 mg diethanolamine per kilogram body weight by the application of 0, 27.5, 55, or 110 mg diethanolamine/mL ethanol solutions, 5 days per week for 103 weeks. Groups of 50 female rats were administered dermal doses of 0, 8, 16, or 32 mg/kg by the application of 0, 13.8, 27.5, or 55 mg/mL solutions, 5 days per week for 103 weeks. Groups of 50 male and 50 female mice were administered dermal doses of 0, 40, 80, or 160 mg/kg by the application of 0, 22.5, 45, or 90 mg/mL solutions, 5 days per week for 103 weeks. Dose volumes were adjusted to provide the appropriate mg/kg dose based on group mean body weights.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Animals were quarantined for 11 days (rats) or 13 days (mice) before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix H).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages and racks were rotated twice weekly. Further details of animal maintenance are given in Table 5. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly; body weights were recorded weekly for the first 13 weeks and monthly thereafter.

A complete necropsy and microscopic examination were performed on all rats and 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 5 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. Step sections were made from the residual kidney wet tissue of male mice because of a slightly increased trend of proliferative lesions in the standard evaluation. Eight additional kidney sections taken at 1 mm intervals were prepared for each male and female. Tissues examined microscopically are listed in Table 5.

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 studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the skin (overall) from the site of application for all rats and mice, the kidney for control and 32 mg/kg female rats, and the kidney (males), liver, and thyroid gland for mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chair, 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 5
Experimental Design and Materials and Methods in the 2-Year Dermal Studies of Diethanolamine

Study Laboratory
Battelle Columbus Laboratories (Columbus, OH)

Strain and Species
Rats: F344/N
Mice: B6C3F$_1$

Animal Source
Taconic Farms (Germantown, NY)

Time Held Before Studies
Rats: 11 days
Mice: 13 days

Average Age When Studies Began
6 weeks

Date of First Dose
Rats: 8 October 1990
Mice: 22 October 1990

Duration of Dosing
5 doses per week for 103 weeks

Date of Last Dose
Rats: 25 September 1992
Mice: 9 October 1992

Necropsy Dates
Rats: 5-7 October 1992
Mice: 19-23 October 1992

Average Age at Necropsy
111 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

TABLE 5
Experimental Design and Materials and Methods in the 2-Year Dermal Studies of Diethanolamine

Diet
NIH-07 open formula 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., Maywood, NJ), changed weekly

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

Cage Filters
DuPont 2024 spun-bonded polyester filters (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks

Racks
Stainless steel (Lab Products, Inc., Maywood, NJ), changed every 2 weeks

Animal Room Environment
Temperature: 17.8°-25.6° C (rats)
20.6°-25.0° C (mice)
Relative humidity: 36%-69% (rats)
35%-69% (mice)
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
Rats: 0, 16, 32, or 64 mg/kg (0, 27.5, 55, or 110 mg/mL; males); and 0, 8, 16, or 32 mg/kg (0, 13.8, 27.5, or 55 mg/mL; females) administered in 95% ethanol; dose volumes were adjusted to provide the appropriate mg/kg dose based on group mean body weights
Mice: 0, 40, 80, or 160 mg/kg (0, 22.5, 45, or 90 mg/mL) administered in 95% ethanol; dose volumes were adjusted to provide the appropriate mg/kg dose based on group mean body weights

Type and Frequency of Observation
Observed twice daily; animals were weighed weekly through week 13 and monthly thereafter; clinical findings were recorded monthly.

Method of Sacrifice
CO_2 anesthetization

Necropsy
Necropsy was performed on all animals.

Histopathology
Complete histopathologic examinations were performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart with aorta, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), 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 or missing 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, A4, B1, B5, C1, C5, D1, and D5 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, B3, C3, and D3) 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, mammary gland, and skin) 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, B3, C3, and D3 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 tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1–P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (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

Although the concurrent control group is always the first and most appropriate control group used for

evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were 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 diethanolamine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated normochromatic erythrocytes in peripheral blood of mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of diethanolamine are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, 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.

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). Survival of dosed male and female rats was similar to that of the vehicle control groups.

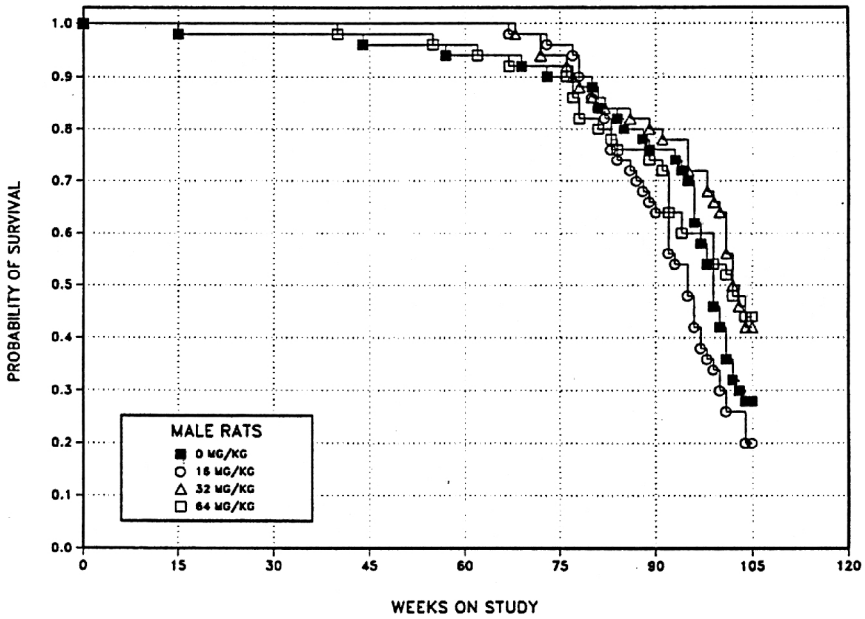
Body Weights and Clinical Findings

Mean body weights of 64 mg/kg males were less than those of the vehicle controls from week 8 to week 89. Mean body weights of 32 mg/kg females were less than those of the vehicle control group after week 97 (Tables 7 and 8 and Figure 2). The only clinical finding attributed to diethanolamine administration was irritation of the skin at the site of application. This effect was dose related (males: vehicle control, 0/50; 16 mg/kg, 1/50; 32 mg/kg, 0/50; 64 mg/kg, 4/50; females: vehicle control, 2/50; 8 mg/kg, 2/50; 16 mg/kg, 2/50; 32 mg/kg, 8/50).

TABLE 6
Survival of Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Male				
Animals initially in study	50	50	50	50
Moribund	31	31	25	22
Natural deaths	5	9	4	6
Animals surviving to study termination	14	10	21	22
Percent probability of survival at end of study[a]	28	20	42	44
Mean survival (days)[b]	651	648	678	655
Survival analysis[c]	P=0.066N	P=0.204	P=0.125N	P=0.279N
	Vehicle Control	**8 mg/kg**	**16 mg/kg**	**32 mg/kg**
Female				
Animals initially in study	50	50	50	50
Moribund	11	16	12	13
Natural deaths	14	5	9	13
Animals surviving to study termination	25	29	29	24
Percent probability of survival at end of study	50	58	58	48
Mean survival (days)	669	689	679	665
Survival analysis	P=0.709	P=0.337N	P=0.448N	P=0.982

[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 dose group is indicated by **N**.



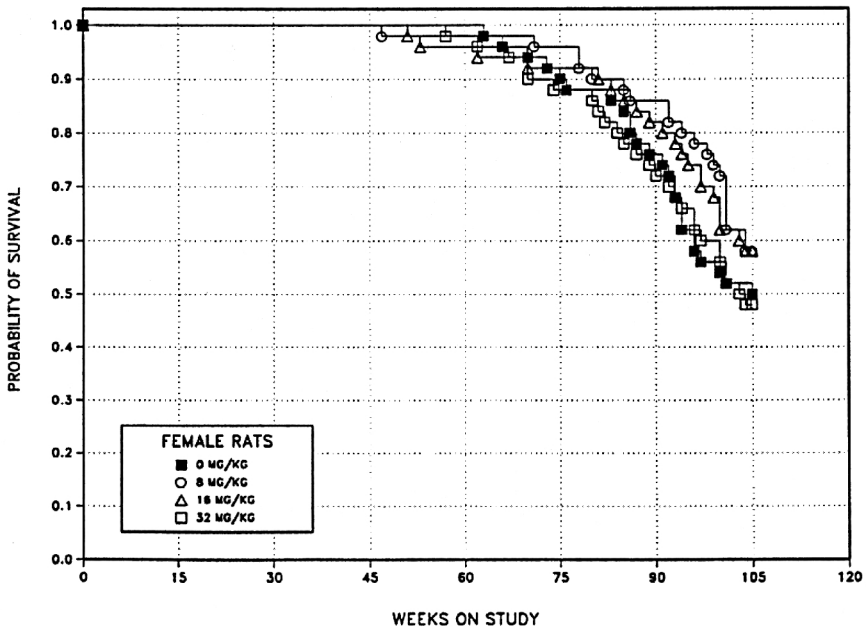


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Diethanolamine Dermally for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Diethanolamine

Weeks on Study	Vehicle Control		16 mg/kg			32 mg/kg			64 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	131	50	133	102	50	130	100	50	130	99	50
2	161	50	165	102	50	161	100	50	158	98	50
3	189	50	193	102	50	188	100	50	183	97	50
4	209	50	212	102	50	207	99	50	202	97	50
5	227	50	229	101	50	222	98	50	218	96	50
6	241	50	240	100	50	236	98	50	229	95	50
7	253	50	253	100	50	250	99	50	240	95	50
8	265	50	267	101	50	260	98	50	250	94	50
9	280	50	280	100	50	274	98	50	263	94	50
10	287	50	287	100	50	280	97	50	268	93	50
11	291	50	293	101	50	285	98	50	275	95	50
12	299	50	303	101	50	294	98	50	281	94	50
13	309	50	312	101	50	303	98	50	291	94	50
17	338	49	339	100	50	327	97	50	317	94	50
21	362	49	360	100	50	345	96	50	334	92	50
25	378	49	374	99	50	364	96	50	352	93	50
29	393	49	394	100	50	382	97	50	369	94	50
33	407	49	404	99	50	391	96	50	377	93	50
37	415	49	409	99	50	399	96	50	384	92	50
41	421	49	418	99	50	408	97	50	392	93	49
45	430	48	426	99	50	413	96	50	397	93	49
49	442	48	436	99	50	426	96	50	406	92	49
53	451	48	443	98	50	434	96	50	411	91	49
57	450	48	445	99	50	436	97	50	413	92	48
61	457	47	452	99	50	443	97	50	418	92	48
65	465	47	456	98	50	444	96	50	421	91	47
69	467	47	459	98	49	447	96	49	423	91	46
73	466	46	459	98	49	450	97	47	422	91	46
77	464	45	458	99	48	447	96	46	419	90	44
81	467	43	451	97	43	446	95	43	420	90	40
85	464	41	453	98	37	448	97	42	420	91	38
89	446	39	436	98	34	443	99	40	412	93	38
93	426	37	425	100	28	429	101	39	409	96	32
97	414	31	414	100	21	418	101	36	403	98	30
101	408	21	414	102	15	392	96	32	395	97	26
104	402	15	393	98	13	390	97	23	389	97	23
Mean for weeks											
1-13	242		244	101		238	98		230	95	
14-52	398		396	99		384	96		370	93	
53-104	446		440	99		433	97		413	93	

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Diethanolamine

Weeks on Study	Vehicle Control		8 mg/kg			16 mg/kg			32 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	105	50	105	100	50	106	101	50	105	101	50
2	123	50	123	100	50	123	100	50	124	100	50
3	135	50	137	101	50	134	99	50	136	100	50
4	144	50	144	100	50	142	99	50	143	99	50
5	150	50	149	100	50	148	99	50	147	98	50
6	156	50	155	99	50	154	99	50	152	98	50
7	160	50	159	99	50	158	98	50	156	97	50
8	165	50	165	100	50	163	99	50	161	98	50
9	168	50	168	100	50	165	98	50	164	98	50
10	172	50	171	99	50	168	97	50	167	97	50
11	173	50	173	100	50	170	98	50	168	97	50
12	175	50	174	99	50	172	98	50	170	97	50
13	178	50	177	100	50	175	98	50	174	98	50
17	190	50	189	99	50	187	99	50	185	97	50
21	196	50	195	99	50	191	97	50	190	97	50
25	204	50	204	100	50	200	98	50	198	97	50
29	212	50	214	101	50	209	98	50	208	98	50
33	217	50	219	101	50	214	99	50	213	98	50
37	223	50	224	100	50	219	99	50	217	98	50
41	230	50	232	101	50	226	99	50	226	99	50
45	235	50	239	102	50	232	99	50	234	99	50
49	247	50	251	101	49	244	99	50	245	99	50
53	256	50	258	101	49	254	99	48	254	99	50
57	261	50	263	101	49	258	99	48	255	98	50
61	270	50	272	101	49	267	99	48	267	99	49
65	277	49	280	101	49	276	100	47	274	99	48
69	282	48	283	101	49	280	99	47	279	99	47
73	281	47	287	102	48	283	101	46	283	101	45
77	285	44	289	101	48	284	99	46	282	99	44
81	291	44	293	101	45	287	99	45	280	96	43
85	292	42	293	100	44	290	99	44	281	96	39
89	291	39	296	102	43	289	99	42	282	97	38
93	292	36	296	102	41	289	99	40	282	97	34
97	300	29	294	98	39	292	97	37	278	93	31
101	306	26	291	95	35	297	97	31	266	87	28
104	301	26	293	97	30	292	97	30	257	85	25
Mean for weeks											
1-13	154		154	100		152	99		151	98	
14-52	217		219	101		214	99		213	98	
53-104	285		285	100		281	99		273	96	

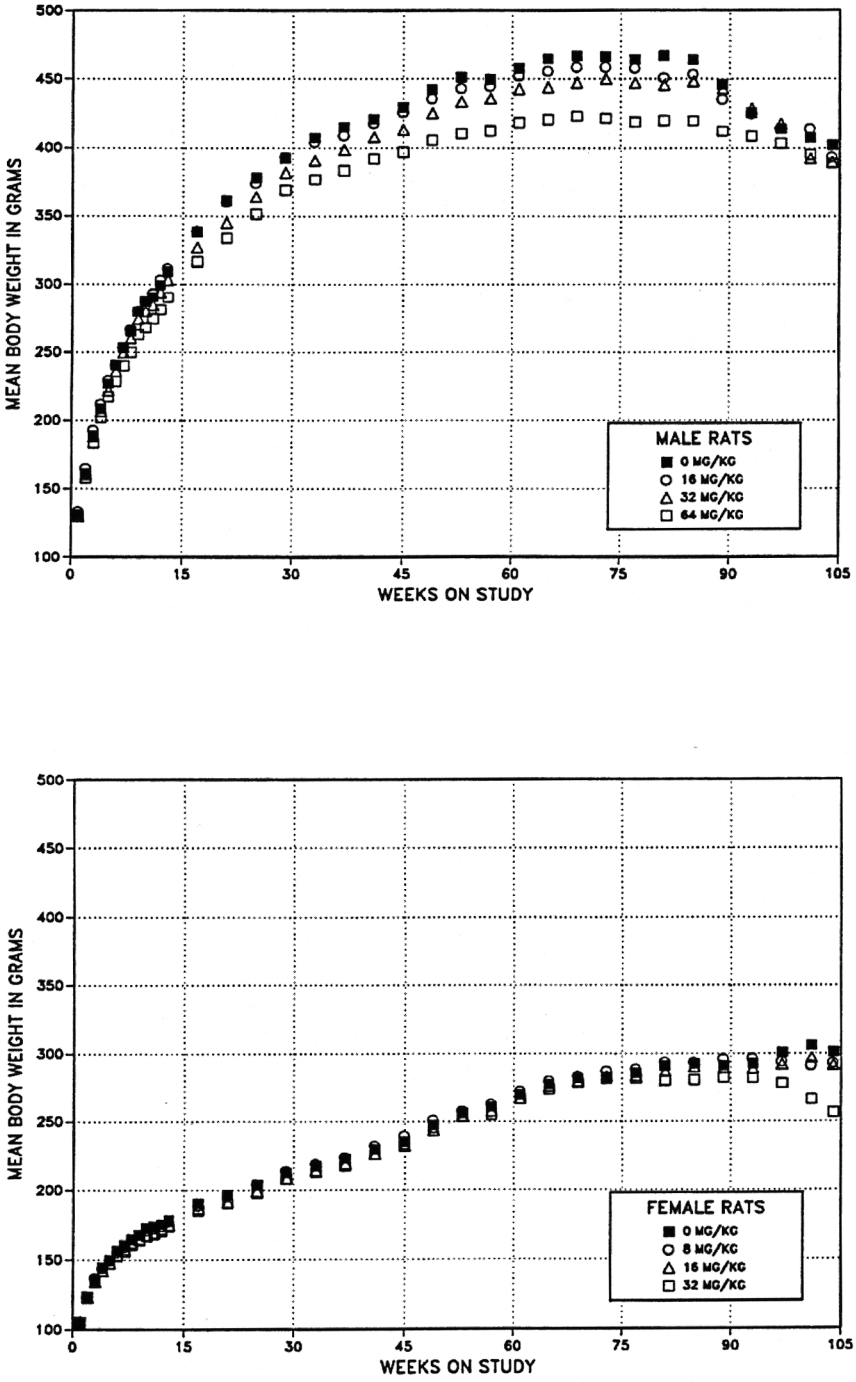


FIGURE 2
Growth Curves for Male and Female Rats Administered Diethanolamine Dermally for 2 Years

Pathology and Statistical Analysis

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

Skin: No biologically significant incidences of skin or subcutaneous neoplasms occurred in the dosed groups. Minimal to mild nonneoplastic lesions occurred at the site of application in the epidermis of dosed male and female rats. One of the most common effects was thickening of the epidermis, or acanthosis. In 64 mg/kg males, the incidence of acanthosis was significantly greater than that in the vehicle control group (Tables 9 and A4). Hyperkeratosis, consisting of an increased amount of keratin on the surface of the skin, was more common in treated females than in males. This lesion was of minimal severity. The incidences of hyperkeratosis in the 32 and 64 mg/kg male groups and in all dosed female groups significantly exceeded those in the vehicle control groups (Tables 9, A4, and B5). Exudate, consisting of focal accumulations of serum and cellular debris on the epidermal surface, occurred at significantly increased incidences in 64 mg/kg males and in all dosed female groups.

TABLE 9
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Dermis, Ulcer[a]	0	0	0	2 (1.0)[b]
Epidermis, Acanthosis	0	2 (1.0)	4 (1.0)	10** (1.1)
Epidermis, Exudate	0	3 (1.0)	2 (1.0)	7* (1.0)
Epidermis, Hyperkeratosis	0	3 (1.0)	5* (1.0)	11** (1.0)
	Vehicle Control	**8 mg/kg**	**16 mg/kg**	**32 mg/kg**
Female				
Number Examined Microscopically	50	50	50	50
Dermis, Ulcer	2 (2.0)	1 (1.0)	1 (3.0)	1 (3.0)
Epidermis, Acanthosis	1 (2.0)	1 (1.0)	4 (1.0)	6 (1.2)
Epidermis, Exudate	1 (1.0)	7* (1.0)	7* (1.0)	7* (1.0)
Epidermis, Hyperkeratosis	3 (1.0)	13* (1.0)	23** (1.0)	23** (1.0)

* Significantly different ($P \le 0.05$) from the vehicle control group by the Poly-3 test
** $P \le 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Kidney: The incidences (vehicle control, 40/50; 8 mg/kg, 47/50; 16 mg/kg, 48/50; 32 mg/kg, 48/50; Table B1) and severities (1.2, 1.5, 1.9, 2.7) of nephropathy in dosed female groups were significantly greater than those in the vehicle controls; however, neither the incidences nor the severities of nephropathy in dosed male rats were significantly different from those in the vehicle controls. Minimal nephropathy consisted of a few scattered tubules with small, basophilic epithelial cells. More severe nephropathy included interstitial fibrosis and loss of nephrons. The severity grades were based on extent of kidney involvement as well as the amount of fibrosis and tubule/nephron loss. One 64 mg/kg male rat had a single renal tubule carcinoma (Table A1).

Liver: There was no neoplastic response in the liver associated with diethanolamine exposure (Tables A1 and B1). The incidences of basophilic foci were significantly decreased in all dosed groups of males and females (males: vehicle control, 15/50; 16 mg/kg, 5/50; 32 mg/kg, 1/50; 64 mg/kg, 2/50; females: 40/50, 31/50, 20/50, 7/50; Tables A4 and B5). The incidences of eosinophilic foci in dosed males were marginally less than that in the vehicle controls (4/50, 2/50, 2/50, 2/50), and the incidences of mixed cell foci in dosed females were somewhat variable (0/50, 3/50, 6/50, 1/50).

Mammary Gland: The incidence of fibroadenoma in 32 mg/kg females was significantly decreased compared to the vehicle control incidence (14/50, 8/50, 9/49, 5/50; Table B3). Incidences of fibroadenoma occurred with a negative trend. The incidences in all dosed groups were less than the historical control range (Table B4).

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 10 and in the Kaplan-Meier survival curves (Figure 3). Survival was similar in dosed male groups and vehicle controls. Survival of dosed female groups was significantly lower than that of the vehicle control group and decreased significantly with increasing dose.

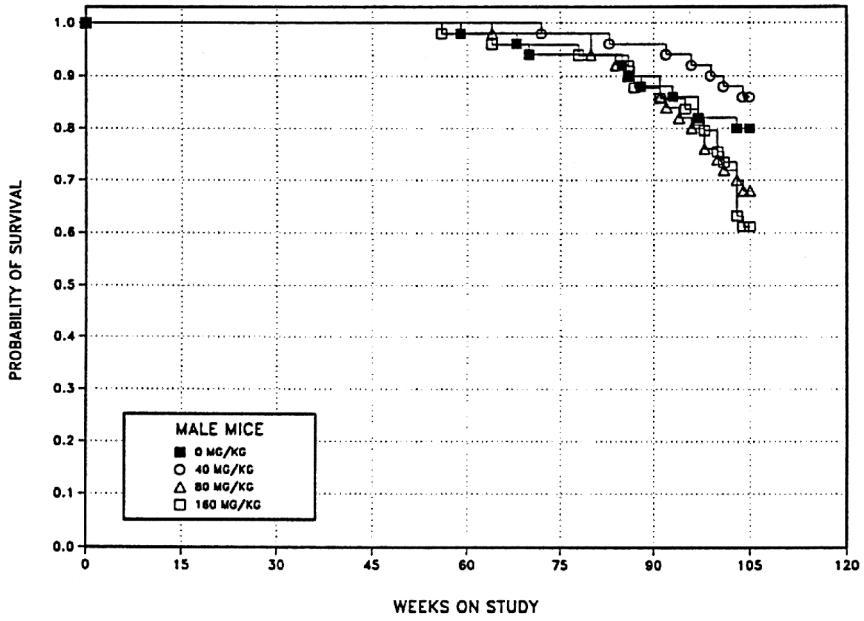
Body Weights

Mean body weights of 80 and 160 mg/kg males were less than those of the vehicle controls after weeks 88 and 77, respectively (Figure 4 and Table 11). Mean body weights of 40 and 80 mg/kg females were less than those of vehicle controls after week 73; mean body weights of 160 mg/kg females were less than those of the vehicle controls after week 53 (Figure 4 and Table 12).

TABLE 10
Survival of Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	3	1	6	10
Natural deaths	7	6	10	9
Animals surviving to study termination	40	43[e]	34	30
Percent probability of survival at end of study[b]	80	86	68	61
Mean survival (days)[c]	701	717	699	687
Survival analysis[d]	P=0.015	P=0.539N	P=0.289	P=0.097
Female				
Animals initially in study	50	50	50	50
Moribund	4	8	9	13
Natural deaths	2	9	8	14
Terminal sacrifice	44	33	33	23[f]
Percent probability of survival at end of study	88	66	66	46
Mean survival (days)	720	669	695	691
Survival analysis	P<0.001	P=0.012	P=0.016	P<0.001

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] 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 lower mortality in a dose group is indicated by **N**.
[e] Includes two animals that died during the last week of the study
[f] Includes one animal that died during the last week of the study



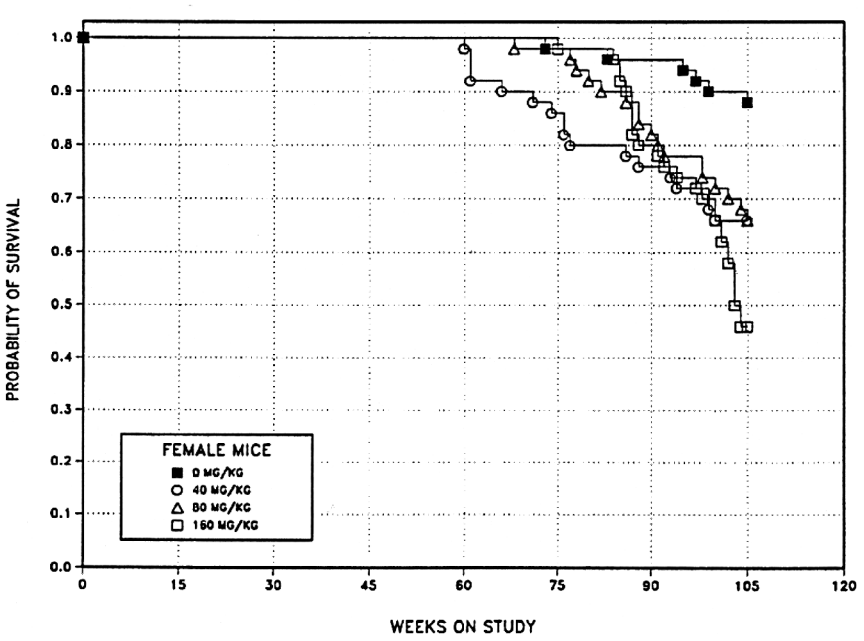


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Diethanolamine Dermally for 2 Years

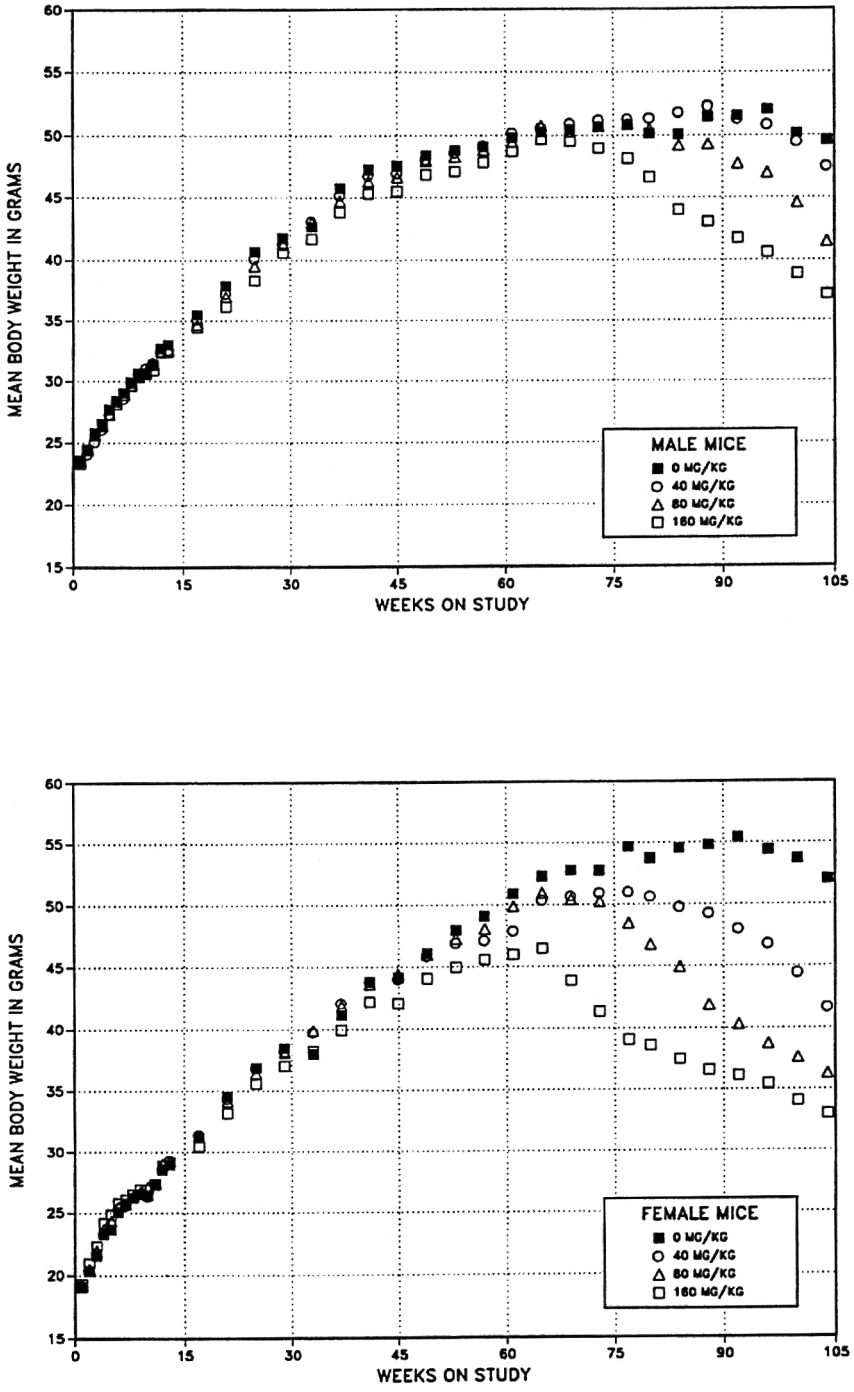


FIGURE 4
Growth Curves for Male and Female Mice Administered Diethanolamine Dermally for 2 Years

TABLE 11
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Diethanolamine

Weeks on Study	Vehicle Control		40 mg/kg			80 mg/kg			160 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	23.6	50	23.4	99	50	23.5	100	50	23.3	99	50
2	24.4	50	24.1	99	50	24.4	100	50	24.4	100	50
3	25.8	50	25.1	97	50	25.6	99	50	25.7	100	50
4	26.4	50	26.1	99	50	26.4	100	50	26.5	100	50
5	27.7	50	27.3	99	50	27.3	99	50	27.3	99	50
6	28.4	50	28.3	100	50	28.3	100	50	28.1	99	50
7	29.0	50	28.5	98	50	28.9	100	50	28.9	100	50
8	29.9	50	29.9	100	50	29.6	99	50	29.7	99	50
9	30.4	50	30.5	100	50	30.4	100	50	30.6	101	50
10	30.6	50	31.1	102	50	30.8	101	50	30.7	100	50
11	31.3	50	31.5	101	50	31.4	100	50	30.9	99	50
12	32.7	50	32.4	99	50	32.5	99	50	32.4	99	50
13	33.0	50	32.5	99	50	32.6	99	50	32.4	98	50
17	35.5	50	35.1	99	50	34.6	98	50	34.4	97	50
21	37.9	50	37.3	98	50	37.0	98	50	36.2	96	50
25	40.7	50	40.1	99	50	39.5	97	50	38.3	94	50
29	41.7	50	41.3	99	50	41.3	99	50	40.6	97	50
33	42.7	50	43.1	101	50	43.0	101	50	41.7	98	50
37	45.8	50	45.2	99	50	44.8	98	50	43.9	96	49
41	47.2	50	46.8	99	50	46.3	98	50	45.3	96	49
45	47.5	50	47.0	99	50	46.7	98	50	45.5	96	49
49	48.4	50	48.0	99	50	48.0	99	50	46.9	97	49
53	48.8	50	48.6	100	50	48.3	99	50	47.1	97	49
57	49.0	50	49.1	100	50	48.8	100	50	47.8	98	48
61	49.8	49	50.2	101	50	49.5	99	50	48.7	98	48
65	50.3	49	50.6	101	50	50.8	101	49	49.7	99	47
69	50.5	48	51.0	101	50	50.3	100	49	49.5	98	47
73	50.7	47	51.2	101	49	50.7	100	49	49.0	97	47
77	50.8	47	51.3	101	49	50.9	100	49	48.1	95	47
80	50.2	47	51.4	102	49	50.5	101	48	46.6	93	46
84	50.1	47	51.8	103	48	49.2	98	46	44.0	88	46
88	51.5	44	52.3	102	48	49.3	96	45	43.1	84	43
92	51.6	44	51.3	99	48	47.7	92	43	41.7	81	42
96	52.1	43	50.9	98	47	47.0	90	40	40.6	78	41
100	50.2	41	49.5	99	45	44.6	89	38	38.9	78	38
104	49.6	40	47.5	96	43	41.5	84	35	37.2	75	30
Mean for weeks											
1-13	28.7		28.5	99		28.6	100		28.5	99	
14-52	43.0		42.7	99		42.4	99		41.4	96	
53-104	50.4		50.5	100		48.5	96		45.1	89	

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Diethanolamine

Weeks on Study	Vehicle Control		40 mg/kg			80 mg/kg			160 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	19.0	50	19.2	101	50	19.2	101	50	19.3	102	50
2	20.4	50	20.4	100	50	20.5	101	50	21.0	103	50
3	21.6	50	21.8	101	50	21.9	101	50	22.3	103	50
4	23.3	50	23.3	100	50	23.7	102	50	24.2	104	50
5	23.7	50	24.1	102	50	24.4	103	50	24.8	105	50
6	25.1	50	25.3	101	50	25.5	102	50	25.8	103	50
7	25.7	50	25.6	100	50	25.7	100	50	26.1	102	50
8	26.2	50	26.2	100	50	26.3	100	50	26.5	101	50
9	26.5	50	26.6	100	50	26.7	101	50	26.9	102	50
10	26.4	50	26.3	100	50	27.1	103	50	26.9	102	50
11	27.2	50	27.3	100	50	27.4	101	50	27.4	101	50
12	28.5	50	28.6	100	50	29.0	102	50	28.9	101	50
13	28.9	50	29.3	101	50	29.2	101	50	29.1	101	50
17	31.2	50	31.4	101	50	31.3	100	50	30.4	97	50
21	34.5	50	34.3	99	50	34.2	99	50	33.2	96	50
25	36.9	50	36.8	100	50	36.4	99	50	35.5	96	50
29	38.4	50	38.2	100	50	38.1	99	50	37.0	96	50
33	38.0	50	39.7	105	50	39.9	105	50	38.2	101	50
37	41.1	50	42.1	102	50	41.9	102	50	39.9	97	50
41	43.8	50	43.8	100	50	43.6	100	50	42.2	96	50
45	44.1	50	44.0	100	50	44.4	101	50	42.1	96	50
49	46.1	50	45.8	99	50	46.0	100	50	44.1	96	50
53	47.9	50	46.9	98	50	47.3	99	50	44.9	94	50
57	49.1	50	47.1	96	50	48.0	98	50	45.6	93	50
61	50.9	50	47.9	94	48	49.9	98	50	46.0	90	50
65	52.3	50	50.3	96	46	50.9	97	50	46.5	89	50
69	52.8	50	50.7	96	45	50.4	96	49	43.9	83	50
73	52.7	50	50.9	97	44	50.3	95	49	41.3	78	50
77	54.6	49	51.0	93	41	48.5	89	49	39.1	72	49
80	53.7	49	50.6	94	40	46.7	87	46	38.6	72	49
84	54.5	48	49.8	91	40	44.9	82	45	37.5	69	49
88	54.8	48	49.3	90	38	41.9	77	44	36.6	67	40
92	55.4	48	48.0	87	38	40.3	73	39	36.1	65	39
96	54.4	47	46.8	86	36	38.7	71	39	35.4	65	37
100	53.6	45	44.4	83	33	37.6	70	36	34.1	64	33
104	52.0	45	41.6	80	33	36.3	70	34	33.0	64	24
Mean for weeks											
1-13	24.8		24.9	100		25.1	101		25.3	102	
14-52	39.3		39.6	101		39.5	101		38.1	97	
53-104	52.8		48.2	91		45.1	85		39.9	76	

Pathology and Statistical Analysis

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

Liver: The incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in all dosed groups of male mice were significantly greater than those in the vehicle control group (Tables 13 and C3). The incidences of hepatocellular carcinoma and hepatoblastoma in 80 and 160 mg/kg males were also significantly increased compared to the vehicle controls. In dosed groups of female mice, the incidences of hepatocellular neoplasms were significantly greater than those in the vehicle control group (Tables 13 and D3). The incidences of hepatocellular neoplasms in all dosed groups of males and females exceeded the historical control ranges (Tables C4a and D4a).

The microscopic appearance of these liver neoplasms was typical of that usually observed in $B6C3F_1$ mice. There was a morphologic continuum from adenoma to carcinoma, with less differentiation and typical trabecular formations in the carcinomas. Carcinomas were often a centimeter or more in diameter, whereas adenomas were generally smaller and more discrete. Both adenomas and carcinomas displaced normal liver parenchyma and neither contained the normal liver lobular architecture. Lung metastases were seen in mice with hepatocellular carcinomas or hepatoblastomas (males: 3/50, 4/50, 9/50, 7/50; females: 0/50, 3/50, 6/50, 1/50; Tables C1 and D1).

Hepatoblastomas often originated within hepatocellular carcinomas and were characterized by well-demarcated, focal areas composed of bundles of deeply basophilic spindle-shaped cells. These cells were presumably poorly differentiated cells, and hepatoblastoma probably was a primitive variant of hepatocellular carcinoma.

The size and multiplicity of neoplasms in treated animals was considerably greater than in the vehicle controls. In many instances, a diagnosis of multiple adenomas in vehicle control mice was indicative of two neoplasms, whereas in dosed mice (especially 160 mg/kg mice), multiple adenomas corresponded to five or more separate neoplasms.

Nonneoplastic lesions were seen only in dosed male and female mice and consisted of cytoplasmic alteration, characterized by mild to moderate enlargement of centrilobular hepatocytes, and syncytial alteration, characterized by scattered hepatocytes with three or more small nuclei (Table C5).

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Cytoplasmic Alteration[a]	1 (2.0)[b]	17** (1.6)	17** (1.9)	12** (2.0)
Syncytial Alteration	0	28 (1.3)	38** (1.7)	23** (2.0)
Hepatocellular Adenoma, Multiple	12/50 (24%)	36/50 (72%)**	47/50 (94%)**	41/50 (82%)**
Hepatocellular Adenoma (includes multiple)[c]				
Overall rate[d]	31/50 (62%)	42/50 (84%)	49/50 (98%)	45/50 (90%)
Adjusted rate[e]	65.0%	86.5%	98.0%	93.5%
Terminal rate[f]	28/40 (70%)	40/43 (93%)	33/34 (97%)	28/30 (93%)
First incidence (days)	411	641	445	386
Poly-3 test[g]	P<0.001	P=0.009	P<0.001	P<0.001
Hepatocellular Carcinoma, Multiple	2/50 (4%)	5/50 (10%)	14/50 (28%)**	17/50 (34%)**
Hepatocellular Carcinoma (includes multiple)[h]				
Overall rate	12/50 (24%)	17/50 (34%)	33/50 (66%)	34/50 (68%)
Adjusted rate	25.1%	34.9%	66.9%	72.3%
Terminal rate	6/40 (15%)	13/43 (30%)	20/34 (59%)	20/30 (67%)
First incidence (days)	485	576	445	446
Poly-3 test	P<0.001	P=0.206	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma (includes multiple)				
Overall rate	39/50 (78%)	47/50 (94%)	50/50 (100%)	49/50 (98%)
Adjusted rate	79.0%	95.3%	100.0%	99.9%
Terminal rate	31/40 (78%)	41/43 (95%)	34/34 (100%)	30/30 (100%)
First incidence (days)	411	576	445	386
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Hepatoblastoma[i]				
Overall rate	0/50 (0%)	2/50 (4%)	8/50 (16%)	5/50 (10%)
Adjusted rate	0.0%	4.2%	17.5%	11.3%
Terminal rate	0/40 (0%)	2/43 (5%)	4/34 (12%)	2/30 (7%)
First incidence (days)	—[j]	729 (T)	633	684
Poly-3 test	P=0.018	P=0.249	P=0.004	P=0.028
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (includes multiple)[k]				
Overall rate	39/50 (78%)	47/50 (94%)	50/50 (100%)	49/50 (98%)
Adjusted rate	79.0%	95.3%	100.0%	99.9%
Terminal rate	31/40 (78%)	41/43 (95%)	34/34 (100%)	30/30 (100%)
First incidence (days)	411	576	445	386
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Female				
Number Examined Microscopically	50	50	50	50
Syncytial Alteration	0	2 (1.5)	17** (1.1)	18** (1.2)
Hepatocellular Adenoma, Multiple	16 (32%)	43 (86%)**	46 (92%)**	45 (90%)**
Hepatocellular Adenoma (includes multiple)[l]				
Overall rate	32/50 (64%)	50/50 (100%)	48/50 (96%)	48/50 (96%)
Adjusted rate	66.1%	100.0%	96.4%	96.4%
Terminal rate	30/44 (68%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma, Multiple	0/50 (0%)	6/50 (12%)*	21/50 (42%)**	26/50 (52%)**
Hepatocellular Carcinoma (includes multiple)[m]				
Overall rate	5/50 (10%)	19/50 (38%)	38/50 (76%)	42/50 (84%)
Adjusted rate	10.4%	43.4%	77.9%	84.9%
Terminal rate	4/44 (9%)	12/33 (36%)	26/33 (79%)	18/23 (78%)
First incidence (days)	729	423	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma (includes multiple)				
Overall rate	33/50 (66%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	68.2%	100.0%	100.0%	100.0%
Terminal rate	31/44 (71%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatoblastoma[n]	0/50 (0%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[o]				
Overall rate	33/50 (66%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	68.2%	100.0%	100.0%	100.0%
Terminal rate	31/44 (71%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Diethanolamine

* 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] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year dermal studies with vehicle control groups (mean ± standard deviation): 118/249 (47.4% ± 8.9%); range, 38%-62%
[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 in animals surviving until the end of the study
[g] In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the 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.
[h] Historical incidence: 54/249 (21.7% ± 2.5%); range, 18%-24%
[i] Historical incidence: 1/249 (0.4% ± 0.9%); range, 0%-2%
[j] Not applicable; no neoplasms in animal group
[k] Historical incidence: 154/249 (61.8% ± 9.1%); range, 56%-78%
[l] Historical incidence: 133/252 (52.8% ± 11.4%); range, 38%-64%
[m] Historical incidence: 35/252 (13.9% ± 7.3%); range, 6%-23%
[n] Historical incidence: 1/252 (0.4% ± 0.9%); range, 0%-2%
[o] Historical incidence: 149/252 (59.1% ± 6.4%; range, 52%-66%

Kidney: The incidences of renal tubule adenoma in males occurred with a positive trend; however, the incidences of carcinoma and hyperplasia did not follow this pattern (Tables 14, C3, and C5). The incidences of adenoma or carcinoma (combined) in male mice exceeded the historical control range (Table C4b). To determine whether additional hyperplasias or neoplasms were present, the kidneys were step sectioned and an extended analysis of proliferative lesions in the kidney was conducted. The combined analysis of single and step sections indicated a dose-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma in male mice. Two additional adenomas were found in the 40 mg/kg group, four in the 80 mg/kg group, and one in the 160 mg/kg group. Additional incidences of hyper-plasia were found in all groups, and the single- and step-section (combined) incidence in the 160 mg/kg group was significantly greater than that in the vehicle control group. Adenomas were focal compressive masses approximately the size of five tubule diameters or greater. Carcinomas were similar morphologically but were relatively large and often showed cellular debris and/or mineralization. Renal tubule neoplasms were located in the cortex and/or outer medulla.

Focal proliferative masses less than the diameter of five tubules, observed in vehicle control and dosed males, were classified as focal hyperplasia (Table 14).

Thyroid Gland: Incidences of follicular cell hyper-plasia were significantly increased in dosed groups (males: vehicle control, 18/50; 40 mg/kg, 22/49; 80 mg/kg, 30/50; 160 mg/kg, 42/50; females: 18/50, 28/50, 32/50, 39/49; Tables C5 and D5). This lesion consisted of focal areas of thyroid gland follicles lined by increased numbers of epithelial cells, which in some instances formed papillary projections. The severity grade for follicular cell hyperplasia (males: 1.6, 1.5, 1.6, 2.2; females: 1.9, 2.0, 1.7, 1.9) was based on the size of the lesion. Incidences of thyroid gland follicular cell adenomas were not increased relative to vehicle controls (males: 4/50, 5/50, 4/50, 2/50; females: 4/50, 9/50, 5/50, 3/49; Tables C3 and D3), and no thyroid gland follicular cell carcinomas were detected in this study.

TABLE 14
Incidences of Renal Tubule Neoplasms and Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Renal Tubule Hyperplasia[a]	1 (3.0)[b]	2 (2.5)	0	3 (2.7)
Renal Tubule Adenoma, Multiple[c]	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Renal Tubule Adenoma (includes multiple)[d]				
Overall rate	1/50 (2%)	4/50 (8%)	6/50 (12%)	6/50 (12%)
Adjusted rate[e]	2.2%	8.3%	13.1%	13.3%
Terminal rate[f]	1/40 (3%)	3/43 (7%)	3/34 (9%)	2/30 (7%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test[g]	P=0.049	P=0.196	P=0.056	P=0.053
Renal Tubule Carcinoma				
(Includes multiple)	2/50 (4%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Renal Tubule Adenoma or Carcinoma (includes multiple)[h]				
Overall rate	3/50 (6%)	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted rate	6.6%	10.4%	13.1%	17.8%
Terminal rate	3/40 (8%)	4/43 (9%)	3/34 (9%)	4/30 (13%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.064	P=0.386	P=0.242	P=0.093
Step Sections (Extended Evaluation)				
Renal Tubule Hyperplasia	2 (1.5)	5 (2.2)	7 (1.3)	7 (2.3)
Renal Tubule Adenoma	0/50 (0%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Renal Tubule Carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Renal Tubule Adenoma or Carcinoma	0/50 (0%)	2/50 (4%)	4/50 (8%)	2/50 (4%)

TABLE 14
Incidences of Renal Tubule Neoplasms and Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Number Examined Microscopically	50	50	50	50
Single Sections and Step Sections (Combined)				
Renal Tubule Hyperplasia	3 (2.0)	7 (2.3)	7 (1.3)	10* (2.4)
Renal Tubule Adenoma, Multiple	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Renal Tubule Adenoma (includes multiple)				
Overall rate	1/50 (2%)	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted rate	2.2%	12.5%	17.5%	15.5%
Terminal rate	1/40 (3%)	5/43 (12%)	5/34 (15%)	3/30 (10%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.046	P=0.065	P=0.016	P=0.028
Renal Tubule Carcinoma (includes multiple)	2/50 (4%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Renal Tubule Adenoma or Carcinoma (includes multiple)				
Overall rate	3/50 (6%)	7/50 (14%)	8/50 (16%)	9/50 (18%)
Adjusted rate	6.6%	14.5%	17.5%	20.0%
Terminal rate	3/40 (8%)	6/43 (14%)	5/34 (15%)	5/30 (17%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.056	P=0.180	P=0.098	P=0.055

* 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] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Number of animals with neoplasm per number of animals with kidney examined microscopically
[d] Historical incidence for 2-year dermal studies with vehicle control groups: 2/299 (0.7% ± 1.0%); range, 0%-2%
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the 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.
[h] Historical incidence: 4/299 (1.3% ± 2.4%); range, 0%-6%

Skin (Site of Application): Hyperkeratosis, acanthosis, and exudate were treatment-related changes in the skin at the site of application. The incidences of hyperkeratosis in all dosed groups except 40 mg/kg females were significantly greater than those in the vehicle control groups (Table 15). Hyperkeratosis was of minimal to mild severity and consisted of increased keratin on the surface. Acanthosis and exudate were observed in a few dosed mice. Acanthosis consisted of increased thickness of the epidermis. Exudate was a mixture of cellular debris and inflammatory cells on the surface of the epidermis, usually mixed with the thickened keratin layer.

Salivary Gland: A significant number of 80 and 160 mg/kg male mice showed a loss of the normal granularity of the cells lining the secretory ducts, which was termed cytoplasmic alteration (1/50, 2/50, 8/50, 23/50; Table C5). The biologic significance of this change is unknown.

TABLE 15
Incidences of Nonneoplastic Lesions of the Epidermis at the Site of Application in Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Acanthosis[a]	0	0	2 (2.0)[b]	4 (1.8)
Exudate	0	0	0	3 (1.3)
Hyperkeratosis	0	13** (1.0)	10** (1.0)	17** (1.1)
Female				
Number Examined Microscopically	50	50	50	50
Acanthosis	0	2 (2.0)	1 (1.0)	2 (2.0)
Exudate	0	1 (4.0)	1 (1.0)	3 (1.7)
Hyperkeratosis	1 (1.0)	3 (2.0)	8* (1.0)	16** (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

GENETIC TOXICOLOGY

Diethanolamine (33 to 3,333 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 when tested with a preincubation protocol in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983; Table E1). No induction of trifluorothymidine resistance was observed in L5178Y mouse lymphoma cells treated with diethanolamine with or without Aroclor 1254-induced male Fisher 344 rat liver S9 (Table E2). In the assay, an increase in pH was noted at all but one (25 nL/mL) of the concentrations tested. Diethanolamine did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Loveday *et al.*, 1989; Tables E3 and E4). In the chromosomal aberration assay, the trial with S9 produced a dose-related increase in the percentage of cells with chromosomal aberrations; however, this increase was not large enough for a positive determination. As with the mouse lymphoma assay, pH increases due to the presence of diethanolamine in the culture medium were noted. Peripheral blood samples collected from male and female mice exposed to 80 to 1,250 mg/kg diethanolamine dermally for 13 weeks showed no increase in the frequency of micronucleated normochromatic erythrocytes (Table E5).

DISCUSSION AND CONCLUSIONS

Diethanolamine is widely used in the preparation of diethanolamides and diethanolamine salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. Because of the extensive human exposure to diethanolamine and diethanolamine condensates of fatty acids and the absence of information concerning the consequences of long-term exposure, diethanolamine, lauric acid diethanolamine condensate, oleic acid diethanolamine condensate, and coconut oil acid diethanolamine condensate were selected for evaluation of carcinogenic potential. The primary route of human exposure to products containing diethanolamides is by contact with the skin. Therefore, this series of studies was conducted by dermal administration.

Diethanolamine administered by topical application to rats at doses of 32, 63, 125, 250, or 500 mg/kg for 13 weeks produced nonneoplastic lesions at several sites (NTP, 1992; Melnick *et al.*, 1994a; Table 3). Minimal nephropathy was present in all groups of rats but was somewhat more severe in dosed females. Renal tubule epithelial cell necrosis was present in the 250 and 500 mg/kg females but was not observed in males, and the incidences of renal tubule mineralization were increased in all groups of dosed females, but this lesion was present only in 500 mg/kg males. Demyelination in the medulla oblongata occurred in males and females that received 500 mg/kg and in seven females that received 250 mg/kg. Acanthosis and hyperkeratosis of the skin at the site of application were present in males administered 63 mg/kg and increased in both incidence and severity at higher doses; however, hyperkeratosis was also present in 32 mg/kg females. Ulcer and chronic inflammation were present in males administered 250 or 500 mg/kg and females administered 125 mg/kg or greater. The toxic response also included a moderate, poorly regenerative, normochromic anemia involving significant changes in red cell parameters at the lowest dose administered (32 mg/kg).

Based on these results, doses of 250 or 500 mg/kg were clearly too high for use in a 2-year study. At 125 mg/kg, acanthosis and hyperkeratosis were present in the skin at the site of application in males and females, but, in addition, females exhibited ulceration and chronic inflammation. Because of the presence of more severe lesions in females at this dose and in males that received higher doses and the potential for skin lesions to progress to ulceration and chronic inflammation over the duration of a 2-year study, the high dose chosen for males was 64 mg/kg. Because females exhibited greater skin sensitivity to diethanolamine than males, 32 mg/kg was selected as the high dose for female rats.

Diethanolamine was also toxic to mice that received 80, 160, 320, 630, or 1,250 mg/kg by topical application for 13 weeks (NTP, 1992; Melnick *et al.*, 1994b; Table 4). The most significant responses occurred in the liver, kidney, and skin. Liver weights were significantly increased in all dosed groups of females and in males treated with 160 mg/kg or greater. Associated with the increase in liver weights were increases in the incidences and severities of cytological alteration of hepatocytes, more so in males than females. Kidney weights were significantly increased in all dosed groups of males and females, and renal tubule epithelial necrosis was present in a few animals treated with 1,250 mg/kg. Acanthosis was present at the site of application in almost all animals treated with diethanolamine. At doses of 320 mg/kg or greater, this was accompanied in some animals by hyperkeratosis and/or chronic inflammation. At 630 mg/kg or greater, ulceration was also present. Based on these results, doses of 320 mg/kg or greater were considered too high for a 2-year study. At 160 mg/kg, acanthosis of the skin and cytological alteration of the liver were minimal in males and females. Therefore, 160 mg/kg was selected as the high dose for the 2-year mouse study.

No neoplasms of the skin associated with exposure to diethanolamine occurred in rats or mice during the 2 year studies. The most significant toxic response in

skin at the site of application was an increased incidence of hyperkeratosis. In rats, the highest incidence (46%) occurred in the 16 and 32 mg/kg groups of females, but the severity was minimal even at 32 mg/kg. In mice, the highest incidence (34%) occurred in the 160 mg/kg group of males. The severity of hyperkeratosis in this group was moderate; however, minimal severity was observed in other groups of males and the 160 mg/kg group of females.

Exposure of mice to diethanolamine for 2 years produced a marked neoplastic response in the liver characterized by significant increases in the incidences and multiplicity of hepatocellular adenoma and hepatocellular carcinoma in males and females. The average size of hepatocellular neoplasms in dosed mice was considerably larger than that of neoplasms in the vehicle controls, and dosed animals with multiple adenomas typically had five or more separate neoplasms, whereas vehicle controls with multiple adenomas usually had only two separate neoplasms. Reduced survival of dosed female mice was considered to be a consequence of the presence of liver neoplasms. The incidences of hepatoblastomas, uncommon phenotypic variants of hepatocellular carcinoma which arise within existing hepatocellular carcinomas, were significantly increased in male mice, but not in females. The incidences of syncytial alteration, a nonneoplastic lesion characterized by the presence of hepatocytes containing multiple (three or more) nuclei, were increased in all groups of dosed mice; this lesion was not present in the controls. A similar lesion was observed in mouse livers during 13-week studies (Melnick *et al.*, 1994b). Centrilobular cytoplasmic alteration was increased in treated males but was not present in females.

The incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) occurred with a positive trend in male mice, but renal tubule carcinoma did not follow the same pattern. An extended evaluation of kidney sections revealed the presence of additional hyperplasias and adenomas in all dosed groups of males and one additional carcinoma in the 160 mg/kg group. Therefore, the extended analysis in male mice confirmed the original observations and, taken together, indicated a treatment- and dose-related increase in the incidences of renal tubule adenoma and adenoma or carcinoma (combined). Although diethanolamine is eliminated in urine as the parent compound, there were no indications that it was nephrotoxic, and neither the incidence nor severity of nephropathy in diethanolamine-treated male mice was increased.

No neoplastic response associated with diethanolamine exposure occurred in rats. In view of the strong toxic response observed in rats during the 13-week studies (NTP, 1992; Melnick *et al.,* 1994a), the absence of response in the 2-year studies is somewhat surprising. However, in rats in the 13-week drinking water and dermal studies, toxic responses at sites other than the site of application (liver, kidney, brain) occurred at doses higher than those used in the 2-year study. In 13-week studies, rat skin was clearly more sensitive to diethanolamine than mouse skin, and doses as low as 125 mg/kg produced ulceration and chronic inflammation. Therefore, it was necessary to use lower doses in the 2-year rat study to avoid excessive dermal toxicity. In addition, the percutaneous absorption of diethanolamine is more rapid through mouse skin than through rat skin. Because the rate of elimination of diethanolamine from rats and mice is very similar, the systemic exposure experienced by rats during the 2-year study was considerably less than that by mice.

Mean body weights of female mice were depressed more than those of male mice, and hepatocellular neoplasms may have contributed to the reduced survival of 160 mg/kg female mice. In addition to the neoplastic response in the liver, increased incidences of renal tubule neoplasms occurred in male mice.

The neoplastic response to diethanolamine exposure involving the liver and kidney of male mice and liver of female mice in the present study is similar to that observed in mice in the 2-year studies of other diethanolamine condensates (NTP 1999a,b). Unreacted diethanolamine was present in varying concentrations in each of the three diethanolamine condensates evaluated in this class study and, therefore, animals in these studies were exposed to a wide range of diethanolamine concentrations. Comparison of the results of these studies reveals a strong association between the concentration of free diethanolamine contaminant present in the different diethanolamide preparations and the incidences of hepatocellular neoplasms in male and female mice and renal tubule neoplasms in male mice. The comparison also reveals a clear gender difference in the response of male and female mice to diethanolamine exposure.

The strongest response occurred in the present study (100% diethanolamine) and involved male and female mice. In addition to increased incidences of liver neoplasms, diethanolamine administration was also associated with significant increases in the multiplicity and size of hepatocellular adenomas and carcinomas.

The next strongest response was observed in the coconut oil acid diethanolamine condensate study (NTP, 1999a) and involved significant increases in hepatocellular neoplasm incidences in mice, but no corresponding increase in the multiplicity or size of neoplasms, as was observed in the diethanolamine study. The incidences of hepatoblastoma were significantly increased in male mice, but not in females. Mean body weights and survival of 200 mg/kg female mice were less than those of the vehicle controls. In addition, the incidences of renal tubule neoplasms were increased in male mice. Based on data provided by the manufacturer, the coconut oil acid diethanolamine condensate contained 18.2% free diethanolamine by weight. Therefore, mice in this study were exposed to 18.2 or 36.4 mg/kg free diethanolamine.

The weakest positive response occurred in the lauric acid diethanolamine condensate (NTP, 1999b) study, in which hepatocellular neoplasms were increased only in female mice. Moreover, although the combined incidence of hepatocellular neoplasms was significantly greater than the combined incidence in the vehicle controls, the incidences of adenomas or carcinomas alone were not significantly increased. Survival of female mice was similar to survival of the vehicle controls, and no response was observed in the kidney of male mice. Based on data provided by the manufacturer, lauric acid diethanolamine condensate contained 0.83% free diethanolamine by weight and, therefore, mice in this study were exposed to 0.83 or 1.66 mg/kg free diethanolamine.

No carcinogenic response occurred in the oleic acid diethanolamine condensate study (NTP, 1999c). Data provided by the manufacturer indicated a free diethanolamine content of 0.19%, less than the 0.83% content for lauric acid diethanolamine condensate. However, in the oleic acid diethanolamine condensate study, mice were given doses of only 15 or 30 mg/kg oleic acid diethanolamine condensate, compared to the other studies in which mice were given doses of 100 or 200 mg/kg of the diethanolamide. Therefore, mice in the oleic acid diethanolamine condensate study were exposed to 0.028 or 0.056 mg/kg of free diethanolamine, the lowest concentration in any of the four studies.

The neoplastic response associated with diethanolamine exposure includes hepatocellular neoplasms in male and female mice and renal tubule neoplasms in male mice. The liver is clearly the most responsive site, and female mice are more sensitive than males. To quantify the association between the incidences of hepatocellular neoplasms and diethanolamine concentration, a logistic regression model was fitted to individual animal neoplasm incidence and survival data. The model predicts the incidence of hepatocellular neoplasms as a function of diethanolamine dose (mg/kg) and survival. This analysis compares the observed liver neoplasm rates in female mice with the rates predicted by the logistic regression model (Figure 5). The close agreement between observed and predicted rates strongly supports the conclusion that the liver neoplasm responses in the diethanolamine study and the three diethanolamine condensate studies are determined primarily by the concentrations of free diethanolamine.

The composition and purity of the bulk diethanolamide preparations used in these studies varied considerably. Lauric acid diethanolamine condensate was approximately 90% lauric acid diethanolamine, 0.83% free diethanolamine, and 9.17% other organic impurities. Oleic acid diethanolamine condensate was 47.5% oleic acid diethanolamine, 0.19% free diethanolamine, approximately 30% other fatty acid alkanolamides, and 22.31% other organic impurities (most probably unreacted fatty acids). Coconut oil itself is a mixture of fatty acids that typically contains as much as 40% lauric acid.

This variable composition was reflected in the composition of coconut oil acid diethanolamine

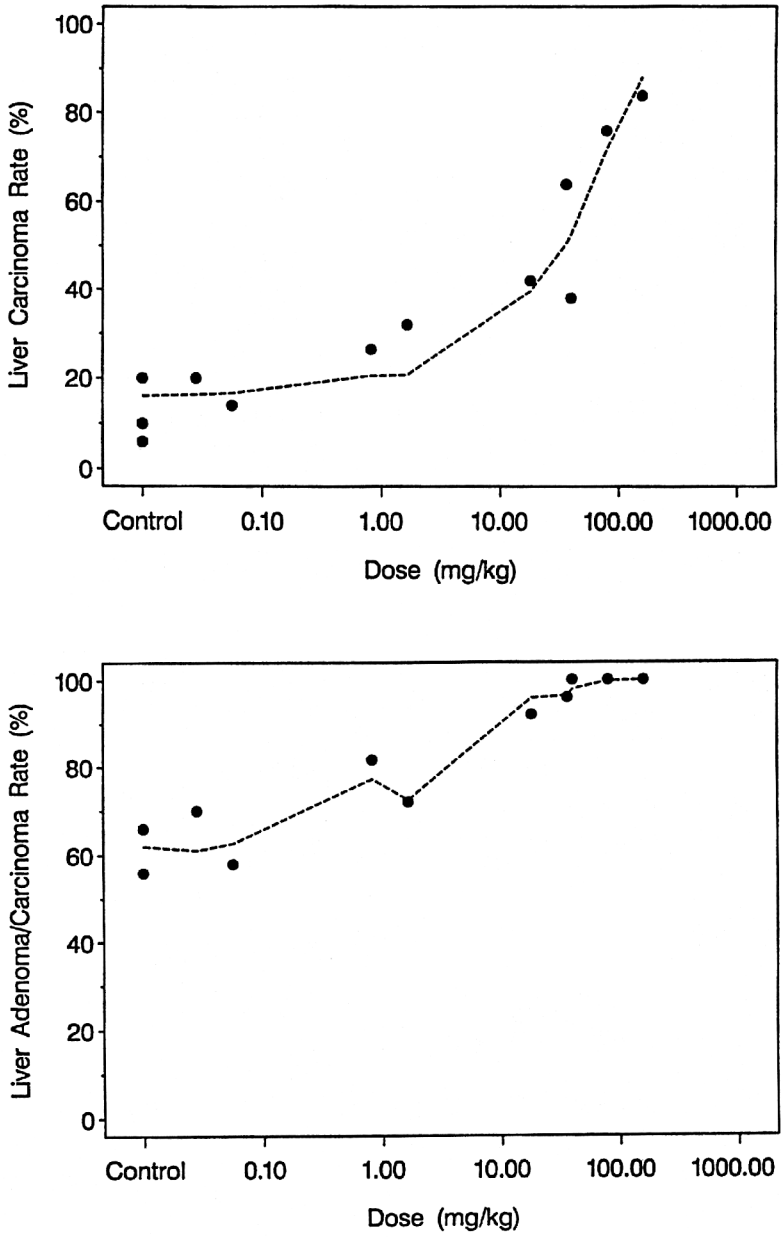


FIGURE 5
Observed and Predicted Liver Neoplasm Incidences in Female B6C3F$_1$ Mice as a Function of Dose and Survival (• = Observed, ----- = Predicted). Predicted rates are based on the logistic regression model, P = 1/[1+exp(T)], where P is the probability of observing a neoplasm. For carcinoma, T = 3.2425 – 0.2920D – 0.00226S, and for adenoma/carcinoma, T = 6.3820 – 0.6822D – 0.00979S, where D = dose$^{1/2}$ in mg diethanolamine/kg body weight and S = survival in days.

condensate in which lauric acid diethanolamine condensate was the major constituent. With animals administered preparations of such widely varying diethanolamide of such widely varying diethanolamide composition, it seems improbable that chance alone could explain the strong correlation between liver neoplasm response and diethanolamine content or the similarity in species, gender, and target tissues specificity observed in the studies with 100% diethanolamine.

The incidences of thyroid gland follicular cell hyperplasia were increased in dosed male and female mice compared to the vehicle controls. Similar increased incidences of follicular cell hyperplasia occurred in male and female mice in the coconut oil acid diethanolamine condensate study and in male mice in the lauric acid diethanolamine condensate study; no increase in the incidences of follicular cell hyperplasia occurred in either male or female mice in the oleic acid diethanolamine condensate study. The incidence of follicular cell hyperplasia appears to be related to the concentration of diethanolamine, although not as strongly as the association between hepatocellular neoplasms and diethanolamine. It is unlikely that the incidences of follicular cell hyperplasia are related to exposure to the diethanolamides because of their varying composition. The lack of an increased incidence of thyroid gland follicular cell neoplasms associated with the increased incidence of follicular cell hyperplasia may be an indication that the increase in the incidence of follicular hyperplasia is a late event occurring near the end of the study.

Absorption, disposition, and metabolism studies of lauric acid diethanolamine condensate indicate that it is well absorbed after dermal or oral administration and is eliminated primarily in the urine as the half amides of succinic and adipic acid (Matthews *et al.*, 1996). No parent diethanolamide, diethanolamine, or diethanolamine-derived metabolites were detected in urine even after oral doses of 1,000 mg/kg. This indicates that there is no metabolic cleavage of the amide linkage of lauric acid diethanolamine and that the metabolism of this compound involves ω-hydroxylation followed by β-oxidation to half amides that are eliminated in urine. Therefore, the source of free diethanolamine in lauric acid diethanolamine condensate and probably also in coconut oil diethanolamine condensate and oleic acid diethanolamine condensate is unreacted material present in the original preparation. No additional bioavailable diethanolamine is released during metabolism of lauric acid diethanolamide, which is quite likely also the case for coconut oil diethanolamine condensate and oleic acid diethanolamine condensate.

Diethanolamine is not a mutagen and is not metabolized to a reactive intermediate; however, it can be converted to a carcinogenic nitrosamine. Nitrosamine formation *in vivo* is thought to occur as a result of a nonenzymatic reaction between an amine and nitrous acid, formed from nitrate in the acid environment of the stomach. The formation of N-nitrosodiethanolamine *in vivo* was demonstrated by Preussmann *et al.* (1981) in rats simultaneously administered sodium nitrate in drinking water (2,000 ppm) and diethanolamine by dermal application of doses comparable to those used in the present rat study (100 to 400 mg/kg). However, N-nitrosodiethanolamine was not detected in groups of rats administered dermal doses of diethanolamine up to 300 mg/kg without nitrite supplementation. Dietary administration of 5,000 ppm diethanolamine, along with 3,000 ppm sodium nitrite, caused a significant increase in the number of γ-glutamyl-transpeptidase (GGT) positive foci in the liver of Wistar rats dosed for 8 weeks. However, 5,000 ppm diethanolamine, without nitrite supplementation, was not associated with any increase in GGT-positive foci (Yamamoto *et al.*, 1995).

Nitrosodiethanolamine was not identified as a urinary metabolite in F344/N rats administered oral (gavage) doses of 200 mg/kg ^{14}C-diethanolamine in repeated-dose studies of 2, 4, or 8 weeks duration, nor was there any significant binding to liver proteins (Matthews *et al.*, 1995). All administered radioactivity was accounted for in excreta as parent compound, free N-methylated diethanolamines, or diethanolamine incorporated into phospholipids. Therefore, nitrosamine formation was not detected in rats given oral doses of diethanolamine twice as large as those administered dermally to high dose rats (64 mg/kg in males; 32 mg/kg in females) in the present study. Because diethanolamine was applied dermally without nitrite supplementation in this study, and dietary nitrate levels were kept within strict limits, it is likely that the concentration of diethanolamine

and nitrite in the stomach contents of rats and mice was too low to support the formation of biologically meaningful quantities of nitrosamine.

N-nitrosodiethanolamine, administered in drinking water at concentrations of 3,900 to 62,500 ppm, produced hepatocellular carcinomas in all male and female F344/N rats after 34 weeks of exposure (Lijinsky *et al.*, 1980). However, no neoplastic response was noted in groups of male and female $B6C3F_1$ mice exposed to the same concentrations of N-nitrosodiethanolamine in drinking water, indicating that F344/N rats are more responsive to the hepatocarcinogenic activity of N-nitroso-diethanolamine than are $B6C3F_1$ mice (Lijinsky *et al.,* 1980). In contrast, in the present studies, exposure to diethanolamine was associated with a strong neoplastic response in the liver of mice but not rats. Moreover, during 13-week drinking water studies (Melnick *et al.*, 1994a), no microscopic lesions were present in the liver of rats administered 5,000 ppm diethanolamine in drinking water for 13 weeks. However, cytologic alteration was present in $B6C3F_1$ mice that received doses as low as 630 ppm, and hepatocellular necrosis was present in groups that received 2,500 ppm or greater for 13 weeks. A similar result was observed in 13-week dermal studies (Melnick *et al.*, 1994b); no microscopic lesions were present in the liver of F344/N rats, even at the highest dose administered (500 mg/kg), while cytologic alteration and hepatocellular necrosis were present in $B6C3F_1$ mice at doses of 80 mg/kg or greater. Therefore, the pattern of response associated with exposure to diethanolamine is distinctly different from that observed after exposure to N-nitrosodiethanolamine.

Diethanolamine, as a structural analogue of ethanol-amine, is incorporated into phospholipid head groups by the same biosynthetic pathways as ethanolamine, leading to the formation of diethanolamine-containing phospholipids. Phospholipids are vital structural components of cell membranes and have a profound effect on membrane properties such as fluidity. Diethanolamine is a longer molecule than ethanolamine and carries an additional hydroxyl group not present in an ethanolamine-containing phospholipid. Both the increased size and additional interaction (hydrogen bonding) through the extra hydroxyl group have the potential to alter the structure and properties of membranes containing diethanol-amine phospholipids.

The primary amino group of the ethanolamine portion of phosphatidyl ethanolamine is methylated to form phosphatidylcholine in a reaction catalyzed by phos-phatidylethanolamine N-methyltransferase, an enzymatic activity found uniquely in the liver. The source of methyl groups for this reaction is *S*-adenosyl-methionine (SAM). Methylation of phosphatidyl ethanolamine to phosphatidylcholine followed by phospholipase cleavage of phosphatidylcholine to choline and diacylglycerol represents the only pathway of *de novo* choline synthesis in mammals. The presence of free N-methyl and N,N-dimethyl-diethanolamine in liver extracts of exposed rats, as well as the presence of methylated diethanolamine head groups in liver phospholipids (Matthews *et al.*, 1995), is an indication that phosphatidyl diethanolamine is methylated and cleaved by the same pathway.

Choline enters hepatocytes by a specific carrier-mediated process (Moseley *et al.*, 1996). The close structural similarity between diethanolamine, methylated diethanolamine, and choline may explain the strong retention of diethanolamine noted by Matthews *et al.* (1995); 70% of diethanolamine equivalents in tissues of animals given daily oral doses for 8 weeks was present as the parent compound. Barbee and Hartung (1979) demonstrated that diethanolamine was a competitive inhibitor of choline incorporation into phosphatidylcholine and a mixed inhibitor of ethanol-amine incorporation into phosphatidylethanolamine in rat liver homogenates. In male Sprague-Dawley rats that consumed 320 mg diethanolamine/kg body weight per day in drinking water, ethanolamine incorporation into phospholipid in liver was reduced to 27% of the control value after 1 week of treatment and choline incorporation was reduced to 41% of the control value after 3 weeks of treatment. This suggests that animals receiving diethanolamine over a long period of time could become choline deficient. Choline deficiency significantly reduces the synthesis of phospholipids in rodents and humans. Since phosphatidylcholine is a major constituent of lipoprotein envelopes, the inability to form these structures inhibits the secretion of triglycerides and leads to the accumulation of fat in the liver, which is easily identified by histologic

examination. Although liver weights were increased in both rats and mice after 13 weeks of exposure to diethanolamine (Melnick *et al.*, 1994a,b), no evidence of fat accumulation was observed in the livers of rats or mice in either the 13-week studies or the present 2-year studies. Therefore, it would appear that exposure to diethanolamine did not produce notable choline deficiency.

Although N,N-dimethyl-diethanolamine can substitute for choline in the biosynthesis of choline-containing phospholipids, it is unclear whether it can substitute for choline in other reactions. Choline is oxidized to betaine in the liver and kidney, and betaine, in turn, serves as a methyl group donor in the conversion of homocysteine to methionine. This reaction establishes a pathway between the methyl groups of choline and the 1-carbon pool. If methylated diethanolamine cannot substitute for choline in methyl group donation, then methylation of diethanolamine would serve to remove methyl groups from the 1-carbon pool. This has the potential of reducing the availability of SAM, the source of methyl groups for the methyltransferases that methylate DNA. Undermethylation of critical genes as a result of reduced availability of SAM could be a factor in the carcinogenic response observed in mice.

Diethanolamine incorporation into phospholipids could also induce toxicity or influence carcinogenic response through its effect on the generation of lipid second messengers from diethanolamine-containing phospholipids. Ceramide is a second messenger generated by the action of sphingomyelinase, a sphingomyelin-specific form of phospholipase C that, upon activation, hydrolyzes phosphocholine from sphingomyelin to yield free phosphocholine and ceramide. Activation of sphingomyelinase is coupled to certain cell surface receptors. Ceramide in turn interacts with specific targets involved in initiating a wide variety of cellular responses (see reviews by Spiegel and Merrill, 1996, and Spiegel *et al.*, 1996). In diethanolamine-treated animals, Matthews *et al.* (1995) found that 93% of diethanolamine incorporated into liver phospholipid was present as ceramide derivatives in which diethanolamine and/or phosphodiethanolamine was incorporated into "sphingomyelin" in place of phosphocholine. The presence of diethanolamide-containing phospholipids in the phospholipid signaling pool used for second messenger generation could have a significant effect on the ability of cells to respond to activation of the sphingomyelin pathway as well as on the character of the response.

Diethanolamine is not a mutagen, it is not metabolized to a mutagen, and it does not interact with DNA. All its biologic effects appear to be associated with its incorporation into phospholipids in place of ethanolamine. The pathways of phospholipid biosynthesis using ethanolamine and choline are highly conserved and essentially the same in all mammals, as is the function of phospholipids as structural components of cell membranes and their role as second messengers. Therefore, it is likely that incorporation of diethanolamine into phospholipids would occur in any suitably exposed mammalian species. Matthews *et al.* (1995) have demonstrated the incorporation of diethanolamine into phospholipids in human liver slices. Therefore, the toxic responses observed in the 13-week studies in rats and mice, as well as the carcinogenic responses that occurred in the 2-year study in mice, indicate potential hazards to humans exposed to diethanolamine.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diethanolamine in male F344/N rats administered 16, 32, or 64 mg/kg diethanolamine or in female F344/N rats administered 8, 16, or 32 mg/kg. There was *clear evidence of carcinogenic activity* of diethanolamine in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males.

Dermal administration of diethanolamine to rats was associated with increased incidences of acanthosis (males only), hyperkeratosis, and exudate of the skin and increased incidences and severities of nephropathy in females. Dermal administration of diethanolamine to mice was associated with increased incidences of cytoplasmic alteration (males only) and syncytial alteration of the liver, renal tubule hyperplasia (males only), thyroid gland follicular cell hyperplasia, and hyperkeratosis of the skin.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DERMAL STUDY OF DIETHANOLAMINE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	31	31	25	22
Natural deaths	5	9	4	6
Survivors				
Terminal sacrifice	14	10	21	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(50)	(50)	(50)	(49)
Carcinoma				1 (2%)
Intestine small, jejunum	(50)	(46)	(48)	(48)
Histiocytic sarcoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma		2 (4%)		1 (2%)
Histiocytic sarcoma			1 (2%)	
Mesentery	(7)	(4)	(8)	(3)
Histiocytic sarcoma			1 (13%)	
Oral mucosa	(7)	(2)	(2)	
Squamous cell carcinoma	1 (14%)	1 (50%)		
Squamous cell papilloma		1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Salivary glands	(50)	(49)	(50)	(50)
Adenoma		1 (2%)		
Schwannoma malignant		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Yolk sac carcinoma, metastatic, tissue NOS	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			2 (4%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	8 (16%)	7 (14%)	4 (8%)	12 (24%)
Bilateral, pheochromocytoma benign	1 (2%)		3 (6%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma	2 (4%)	1 (2%)	1 (2%)	
Parathyroid gland	(46)	(49)	(48)	(47)
Adenoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(49)
Astrocytoma malignant, metastatic, brain	1 (2%)			
Pars distalis, adenoma	32 (64%)	39 (78%)	37 (74%)	27 (55%)
Pars distalis, adenoma, multiple			2 (4%)	5 (10%)
Pars distalis, carcinoma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(49)
Adenoma			1 (2%)	
Carcinoma			1 (2%)	
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	6 (12%)	2 (4%)	5 (10%)	6 (12%)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma	1 (2%)	2 (4%)		
General Body System				
Tissue NOS	(1)			
Yolk sac carcinoma	1 (100%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Preputial gland	(50)	(50)	(49)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	12 (24%)	9 (18%)	13 (26%)	10 (20%)
Interstitial cell, adenoma	20 (40%)	10 (20%)	15 (30%)	16 (32%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymph node	(4)	(4)	(5)	(2)
Deep cervical, bronchial, mediastinal, leukemia mononuclear		1 (25%)		
Deep cervical, mediastinal, carcinoma, metastatic, thyroid gland			1 (20%)	
Mediastinal, histiocytic sarcoma			1 (20%)	
Thoracic, schwannoma malignant				1 (50%)
Lymph node, mandibular	(49)	(48)	(50)	(49)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Fibrosarcoma		1 (2%)		
Thymus	(47)	(48)	(48)	(47)
Histiocytic sarcoma			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Integumentary System				
Mammary gland	(46)	(48)	(45)	(42)
Adenoma				1 (2%)
Carcinoma			1 (2%)	
Fibroadenoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Keratoacanthoma	2 (4%)	1 (2%)		
Schwannoma malignant			1 (2%)	1 (2%)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma		1 (2%)	1 (2%)	
Sebaceous gland, adenoma	2 (4%)			
Sebaceous gland, skin, site of application, adenoma			1 (2%)	
Skin, site of application, keratoacanthoma		1 (2%)		
Subcutaneous tissue, fibroma		1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, schwannoma malignant				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	2 (4%)	1 (2%)		
Skeletal muscle		(1)		
Histiocytic sarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)			
Spinal cord	(2)		(1)	(1)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Histiocytic sarcoma, metastatic, pituitary gland		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Yolk sac carcinoma, metastatic, tissue NOS	1 (2%)			
Nose	(50)	(50)	(50)	(49)
Chondroma		1 (2%)		
Special Senses System				
Harderian gland	(3)			
Squamous cell carcinoma, metastatic, oral mucosa	1 (33%)			
Zymbal's gland		(3)	(1)	(2)
Carcinoma		2 (67%)	1 (100%)	1 (50%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Nephroblastoma	1 (2%)			
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(48)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Leukemia mononuclear	23 (46%)	14 (28%)	13 (26%)	18 (36%)
Lymphoma malignant	1 (2%)			
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	49	49	47
Total primary neoplasms	126	107	107	112
Total animals with benign neoplasms	47	46	48	45
Total benign neoplasms	90	78	86	88
Total animals with malignant neoplasms	32	23	19	22
Total malignant neoplasms	36	29	21	24
Total animals with metastatic neoplasms	5	3	1	
Total metastatic neoplasms	7	3	1	

[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 Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	1 0 1	3 0 2	3 0 4	4 7 9	5 0 7	5 6 0	5 6 1	5 6 1	5 8 2	5 9 5	6 1 0	6 1 9	6 4 5	6 5 3	6 6 3	6 6 6	6 7 0	7 0 0	7 0 0	7 3 3	6 7 4	6 8 0	6 8 3	6 8 7	6 8 7
Carcass ID Number	0 2 3	0 0 5	0 0 3	0 0 2	0 3 9	0 4 9	0 0 1	0 1 3	0 1 8	0 2 9	0 1 0	0 2 7	0 2 8	0 3 4	0 4 1	0 3 6	0 0 9	0 1 7	0 2 4	0 4 2	0 3 2	0 3 3	0 0 7	0 1 9	0 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+	+							+				+						+				
Oral mucosa														+							+	+			
Squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel											+											+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Yolk sac carcinoma, metastatic, tissue NOS							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign												X		X	X									X	
Bilateral, pheochromocytoma benign							X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant, metastatic, brain																									
Pars distalis, adenoma				X	X	X	X			X		X				X		X	X	X		X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X												X			X
Follicular cell, adenoma																				X					
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS							+																		
Yolk sac carcinoma							X																		

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	6 8 7	6 8 9	6 9 4	6 9 6	7 0 2	7 0 2	7 0 2	7 0 9	7 1 0	7 1 7	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 1	0 3 5	0 3 8	0 3 7	0 1 4	0 2 1	0 4 3	0 2 5	0 4 4	0 1 1	0 1 2	0 0 4	0 0 6	0 0 8	0 1 2	0 1 5	0 1 6	0 2 0	0 3 0	0 4 0	0 4 5	0 4 6	0 4 7	0 4 8	0 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+	+																7
Oral mucosa					+	+			+							+										7
Squamous cell carcinoma						X																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+												+													4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla										X																1
Yolk sac carcinoma, metastatic, tissue NOS																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant										X																1
Pheochromocytoma benign		X							X										X					X		8
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X	X													3
Carcinoma														X											X	2
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Adenoma											X															1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant, metastatic, brain												X														1
Pars distalis, adenoma		X	X	X		X	X	X		X	X		X	X	X	X	X		X	X	X		X	X		32
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X																	X			X		6
Follicular cell, adenoma																										1
Follicular cell, carcinoma			X																							1
General Body System																										
Tissue NOS																										1
Yolk sac carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	1 0 1	3 0 2	3 0 4	4 7 9	5 0 7	5 6 0	5 6 1	5 6 1	5 8 2	5 9 5	6 1 0	6 1 9	6 4 5	6 5 3	6 6 3	6 6 6	6 7 0	7 7 0	7 7 0	7 7 3	6 7 4	6 8 0	6 8 3	6 8 7	6 8 7
Carcass ID Number	0 2 3	0 0 5	0 0 3	0 0 2	0 3 9	0 4 9	0 0 1	0 1 3	0 1 8	0 2 9	0 1 0	0 2 7	0 2 8	0 3 4	0 4 1	0 3 6	0 0 9	0 1 7	0 2 4	0 4 2	0 3 2	0 3 3	0 0 7	0 1 9	0 2 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X							X	X					X		X		
Interstitial cell, adenoma									X		X	X	X				X		X			X			X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																				+	+	+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Sebaceous gland, adenoma											X									X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Yolk sac carcinoma, metastatic, tissue NOS							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland							+										+								
Squamous cell carcinoma, metastatic, oral mucosa																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	6 8 7	6 8 9	6 9 4	6 9 6	7 0 2	7 0 2	7 0 2	7 0 9	7 1 0	7 1 7	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 1	0 3 5	0 3 8	0 3 7	0 1 4	0 2 1	0 4 3	0 2 5	0 4 4	0 1 1	0 2 2	0 0 4	0 0 6	0 0 8	0 1 2	0 1 5	0 1 6	0 2 0	0 3 0	0 4 0	0 4 5	0 4 6	0 4 7	0 4 8	0 5 0	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X						X			X				X		X				X			X	12
Interstitial cell, adenoma	X					X	X	X		X	X			X					X	X	X		X	X		20
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																									+	4
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma																				X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X	X																				2
Sebaceous gland, adenoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma			X																							2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant												X														1
Peripheral nerve				+																						2
Spinal cord				+																						2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma malignant, metastatic, adrenal medulla										X																1
Yolk sac carcinoma, metastatic, tissue NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+																				3
Squamous cell carcinoma, metastatic, oral mucosa						X																				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	1 0 1	3 0 2	3 0 4	4 7 9	5 0 7	5 6 0	5 6 1	5 6 1	5 8 2	5 9 5	6 1 0	6 1 9	6 4 5	6 5 3	6 6 3	6 6 6	6 7 0	7 0 0	7 0 0	7 3 3	6 7 4	6 8 0	6 8 3	6 8 7	6 8 7
Carcass ID Number	0 2 3	0 0 5	0 0 3	0 0 2	0 3 9	0 4 9	0 0 1	0 1 3	0 1 8	0 2 9	0 1 0	0 2 7	0 2 8	0 3 4	0 4 1	0 3 6	0 0 9	0 1 7	0 2 4	0 4 2	0 3 2	0 3 3	0 0 7	0 1 9	0 2 6
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X		X	X	X	X		X	X	X		X	X			X		X	X	
Lymphoma malignant																				X					
Mesothelioma malignant														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	6 8 7	6 8 9	6 9 4	6 9 6	7 0 2	7 0 2	7 0 2	7 0 9	7 1 0	7 1 7	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 1	0 3 5	0 3 8	0 3 7	0 1 4	0 2 1	0 4 3	0 2 5	0 4 4	0 1 1	0 2 2	0 0 4	0 0 6	0 0 8	0 1 2	0 1 5	0 1 6	0 2 0	0 3 0	0 4 0	0 4 5	0 4 6	0 4 7	0 4 8	0 5 0	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nephroblastoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X						X	X					X	X			X	X			X		X			23
Lymphoma malignant																											1
Mesothelioma malignant			X																								2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	4 6 3	5 0 9	5 3 8	5 4 1	5 4 2	5 5 4	5 6 0	5 6 2	5 7 2	5 7 6	5 7 7	5 7 7	5 8 4	5 9 9	6 0 6	6 1 0	6 1 9	6 2 5	6 3 8	6 3 9	6 4 0	6 4 2	6 4 8	6 6 1	6 6 2
Carcass ID Number	0 8 2	1 0 0	0 5 6	0 8 7	0 7 8	0 5 9	0 9 5	0 8 6	0 7 9	0 9 2	0 7 0	0 7 4	0 9 4	0 8 9	0 6 4	0 6 5	0 5 5	0 6 7	0 8 4	0 9 3	0 8 1	0 9 1	0 9 7	0 5 8	0 7 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery								+						+								+			
Mesothelioma malignant, metastatic, epididymis																									
Oral mucosa																									
Squamous cell carcinoma																									
Squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Schwannoma malignant															X										
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign	X																X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
C-cell, carcinoma																		X							
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma					X						X										X			X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	6 6 3	6 6 6	6 7 0	6 7 0	6 7 3	6 7 8	6 8 1	6 8 8	6 9 4	6 9 5	7 0 2	7 0 4	7 2 2	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 5 7	0 6 0	0 6 6	0 8 5	0 8 3	0 9 9	0 6 1	0 8 8	0 7 2	0 9 6	0 7 7	0 5 1	0 5 3	0 5 2	0 7 3	0 5 4	0 6 2	0 6 3	0 6 6	0 6 8	0 6 9	0 7 1	0 8 0	0 9 0	0 9 8	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X					X															2
Mesentery																							+		4
Mesothelioma malignant, metastatic, epididymis																							X		1
Oral mucosa		+			+																				2
Squamous cell carcinoma					X																				1
Squamous cell papilloma		X																							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X	1
Schwannoma malignant																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Blood vessel						+				+	+														3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X							X		X			X				X					7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Carcinoma								X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X	X	X	X	X	X	X			X	X	X	X	X	X	X			X	X	39
Pars distalis, carcinoma													X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																			X						2
C-cell, carcinoma																									1
Follicular cell, carcinoma				X				X																	2
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X	X										X		X			X		X		X	9
Interstitial cell, adenoma									X	X			X				X		X			X				10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	4 6 3	5 0 9	5 3 8	5 4 1	5 4 2	5 5 4	5 6 0	5 6 2	5 7 2	5 7 6	5 7 7	5 7 7	5 8 4	5 9 9	6 0 6	6 1 0	6 1 9	6 2 5	6 3 8	6 3 9	6 4 0	6 4 2	6 4 8	6 6 1	6 6 2
Carcass ID Number	0 8 2	1 0 0	0 5 6	0 8 7	0 7 8	0 5 9	0 9 5	0 8 6	0 7 9	0 9 2	0 7 0	0 7 4	0 9 4	0 8 9	0 8 4	0 6 5	0 5 5	0 6 7	0 8 4	0 8 9	0 8 1	0 9 1	0 9 7	0 5 8	0 7 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+								+						+			
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Skin, site of application, keratoacanthoma																X									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X																								
Skeletal muscle																									
Histiocytic sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma, metastatic, pituitary gland																									
Osteosarcoma, metastatic, bone	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland				+	+						+														
Carcinoma				X							X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear						X		X								X					X	X	X		
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	6 6 3	6 6 6	6 7 0	6 7 0	6 7 3	6 7 8	6 8 1	6 8 8	6 9 4	6 9 5	7 0 2	7 0 4	7 2 2	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 5 7	0 6 0	0 6 6	0 8 5	0 8 3	0 9 9	0 6 1	0 8 8	0 7 2	0 9 6	0 7 7	0 5 1	0 5 3	0 5 2	0 7 3	0 5 4	0 6 2	0 6 3	0 6 6	0 6 8	0 6 9	0 7 1	0 8 0	0 9 0	0 9 8	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+																						4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma				X																					1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma											X														1
Squamous cell papilloma																				X					1
Skin, site of application, keratoacanthoma																									1
Subcutaneous tissue, fibroma														X											1
Subcutaneous tissue, fibrosarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																									1
Skeletal muscle													+												1
Histiocytic sarcoma													X												1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma											X														1
Histiocytic sarcoma, metastatic, pituitary gland													X												1
Osteosarcoma, metastatic, bone																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondroma													X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye				+											+										2
Zymbal's gland																									3
Carcinoma																									2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X												1
Leukemia mononuclear	X		X					X			X			X		X						X	X		14
Mesothelioma malignant																							X		1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	4 7 1	4 9 9	5 0 4	5 2 7	5 3 3	5 4 2	5 5 6	5 6 8	5 9 9	6 1 8	6 3 5	6 5 9	6 6 3	6 6 4	6 8 1	6 8 1	6 8 9	6 9 4	7 0 2	7 0 2	7 0 2	7 0 2	7 0 9	7 1 0	7 1 0
Carcass ID Number	1 2 7	1 2 4	1 2 3	1 1 9	1 3 1	1 1 6	1 4 1	1 3 0	1 2 5	1 0 1	1 3 9	1 2 8	1 1 2	1 1 8	1 0 8	1 1 4	1 0 5	1 1 1	1 0 3	1 0 9	1 2 1	1 4 6	1 1 5	1 3 7	1 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Mesentery		+		+			+	+					+	+	+										
Histiocytic sarcoma							X																		
Oral mucosa																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X	X											
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign					X															X					
Bilateral, pheochromocytoma benign											X							X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma													X												
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X		X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X
Pars distalis, adenoma, multiple		X																							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma															X										
C-cell, adenoma								X																	
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X													X	
Interstitial cell, adenoma		X					X						X			X	X				X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	715	715	722	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	11 3	11 2 0	11 4 7	11 0 7	11 0 2	11 0 4	11 0 6	11 1 0	11 1 7	11 2 2	11 2 6	11 2 9	11 3 2	11 3 3	11 3 4	11 3 5	11 3 6	11 3 8	11 4 0	11 4 2	11 4 3	11 4 4	11 4 5	11 4 8	11 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery	+																									8
Histiocytic sarcoma																										1
Oral mucosa										+																2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue														+												1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X											X	4
Bilateral, pheochromocytoma benign				X																						3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X		X	X	X	X		X	X	X	X		X	X			X			X	X	37
Pars distalis, adenoma, multiple																							X			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
C-cell, adenoma			X						X					X		X										5
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma						X		X	X	X			X				X	X	X			X	X	X		13
Interstitial cell, adenoma		X		X	X		X				X			X	X	X					X					15

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	4 7 1	4 9 9	5 0 4	5 2 7	5 3 3	5 4 2	5 5 6	5 6 8	5 9 9	6 1 8	6 3 5	6 5 9	6 6 3	6 6 4	6 8 1	6 8 1	6 8 9	6 9 4	7 0 2	7 0 2	7 0 2	7 0 2	7 0 9	7 1 0	7 1 0
Carcass ID Number	1 2 7	1 2 4	1 2 3	1 1 9	1 3 1	1 1 6	1 4 1	1 3 0	1 2 5	1 0 1	1 3 9	1 2 8	1 1 2	1 1 8	1 0 8	1 1 4	1 0 5	1 1 1	1 0 3	1 0 9	1 2 1	1 4 6	1 1 5	1 3 7	1 5 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymph node		+					+								+										
Deep cervical, mediastinal, carcinoma, metastatic, thyroid gland															X										
Mediastinal, histiocytic sarcoma							X																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																								X	
Squamous cell carcinoma																									
Squamous cell papilloma																									
Sebaceous gland, skin, site of application, adenoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+			+					
Zymbal's gland																			+						
Carcinoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Leukemia mononuclear		X		X		X											X	X	X	X					
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	7 1 5	7 1 5	7 2 2	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 1 3	1 2 0	1 4 7	1 0 7	1 0 2	1 0 4	1 0 6	1 1 0	1 1 7	1 2 2	2 2 6	2 2 9	3 2	3 3	3 4	3 5	3 6	3 8	4 0	4 2	4 3	4 4	4 5	4 8	4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node		+																	+							5
Deep cervical, mediastinal, carcinoma, metastatic, thyroid gland																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	45
Carcinoma									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Squamous cell carcinoma																							X			1
Squamous cell papilloma							X																			1
Sebaceous gland, skin, site of application, adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X		X		X															X	X			X	13
Mesothelioma malignant		X																								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 64 mg/kg

Number of Days on Study	2 7 7	3 7 9	4 3 1	4 6 5	5 3 0	5 3 3	5 3 3	5 4 1	5 4 2	5 6 1	5 7 7	5 8 7	6 2 1	6 3 2	6 4 0	6 4 1	6 4 2	6 4 3	6 5 3	6 5 6	6 8 8	6 8 8	6 8 9	7 0 1	7 0 9
Carcass ID Number	1 6 1	1 9 9	1 5 5	1 9 1	1 6 8	1 7 2	1 8 3	1 9 7	1 7 3	1 8 8	1 6 5	1 6 3	1 6 7	1 5 8	1 9 2	1 7 4	1 8 7	1 7 9	2 0 0	1 7 6	1 7 7	1 9 4	1 6 0	1 9 9	1 5 9	1 8 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X																					
Mesentery														+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel														+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X			X											X	X	X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X		X			X	X	X	X			X	X	X	X	X	X	X		
Pars distalis, adenoma, multiple					X		X																	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma					X																				
C-cell, adenoma				X																				X	X
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																							X		X
Interstitial cell, adenoma				X	X						X				X					X	X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 64 mg/kg

Number of Days on Study	709	722	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	19 5	17 1	16 6	15 1	15 2	15 3	15 4	15 6	15 7	16 2	16 4	16 9	17 0	17 5	17 8	18 0	18 1	18 2	18 4	18 5	18 6	19 0	19 3	19 6	19 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery								+							+											3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X	X		X						X			X				X							X		12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X	X	X								X		X	X		X	X	X		X			27
Pars distalis, adenoma, multiple								X										X								5
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma																										1
C-cell, adenoma	X										X			X												6
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X			X								X										4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X							X	X		X									X	X	X	X	10
Interstitial cell, adenoma				X		X	X		X						X		X	X	X	X	X					16

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 64 mg/kg

Number of Days on Study	2 7 7	3 7 9	4 3 1	4 6 5	5 3 0	5 3 3	5 3 3	5 4 1	5 4 2	5 6 1	5 7 7	5 8 7	6 2 1	6 3 2	6 4 0	6 4 1	6 4 2	6 4 3	6 5 3	6 5 6	6 8 8	6 8 8	6 8 9	7 0 1	7 0 9
Carcass ID Number	1 6 1	1 9 9	1 5 5	1 9 1	1 6 8	1 7 2	1 8 3	1 9 7	1 7 3	1 8 8	1 6 5	1 6 3	1 6 7	1 5 8	1 9 2	1 7 4	1 8 7	1 7 9	2 0 0	1 7 6	1 7 7	1 9 4	1 6 0	1 5 9	1 8 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Thoracic, schwannoma malignant																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																	X								
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, schwannoma malignant											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																+									
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+						+																		
Zymbal's gland							+															+			
Carcinoma							X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X			X	X				X	X		X			X	X		X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethanolamine: 64 mg/kg

Number of Days on Study	709	722	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	19 5	17 1	16 6	15 1	15 2	15 3	15 4	15 6	15 7	16 2	16 4	16 9	17 0	17 5	17 8	18 0	18 1	18 2	18 4	18 5	18 6	19 0	19 3	19 6	19 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+								+																	2
Thoracic, schwannoma malignant									X																	1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma				X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Subcutaneous tissue, fibroma	X																									1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Zymbal's gland																										2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X								X						X	X						18

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	9/50 (18%)	7/50 (14%)	7/50 (14%)	12/50 (24%)
Adjusted rate[b]	22.3%	18.5%	16.3%	29.6%
Terminal rate[c]	2/14 (14%)	2/10 (20%)	2/21 (10%)	5/22 (23%)
First incidence (days)	561	463	533	533
Poly-3 test[d]	P=0.214	P=0.447N	P=0.340N	P=0.309
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	10/50 (20%)	7/50 (14%)	7/50 (14%)	12/50 (24%)
Adjusted rate	24.8%	18.5%	16.3%	29.6%
Terminal rate	2/14 (14%)	2/10 (20%)	2/21 (10%)	5/22 (23%)
First incidence (days)	561	463	533	533
Poly-3 test	P=0.289	P=0.346N	P=0.247N	P=0.404
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	7.8%	2.7%	2.4%	5.1%
Terminal rate	2/14 (14%)	0/10 (0%)	1/21 (5%)	1/22 (5%)
First incidence (days)	687	638	729 (T)	653
Poly-3 test	P=0.456N	P=0.324N	P=0.278N	P=0.495N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.9%	5.4%	4.8%	5.1%
Terminal rate	4/14 (29%)	0/10 (0%)	1/21 (5%)	1/22 (5%)
First incidence (days)	687	638	663	653
Poly-3 test	P=0.170N	P=0.233N	P=0.183N	P=0.209N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	32/50 (64%)	39/50 (78%)	39/50 (78%)	32/49 (65%)
Adjusted rate	72.5%	83.1%	79.9%	70.6%
Terminal rate	10/14 (71%)	8/10 (80%)	15/21 (71%)	12/21 (57%)
First incidence (days)	479	463	471	431
Poly-3 test	P=0.308N	P=0.146	P=0.265	P=0.516N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	32/50 (64%)	40/50 (80%)	39/50 (78%)	32/49 (65%)
Adjusted rate	72.5%	85.2%	79.9%	70.6%
Terminal rate	10/14 (71%)	8/10 (80%)	15/21 (71%)	12/21 (57%)
First incidence (days)	479	463	471	431
Poly-3 test	P=0.272N	P=0.089	P=0.265	P=0.516N
Preputial Gland: Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/49 (2%)	4/50 (8%)
Adjusted rate	2.6%	2.7%	2.5%	10.3%
Terminal rate	1/14 (7%)	0/10 (0%)	1/20 (5%)	3/22 (14%)
First incidence (days)	729 (T)	688	729 (T)	701
Poly-3 test	P=0.071	P=0.749	P=0.749N	P=0.180
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	5.2%	8.2%	2.4%	0.0%
Terminal rate	0/14 (0%)	1/10 (10%)	1/21 (5%)	0/22 (0%)
First incidence (days)	702	610	729 (T)	—[e]
Poly-3 test	P=0.099N	P=0.477	P=0.475N	P=0.236N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	5.2%	8.2%	4.8%	0.0%
Terminal rate	0/14 (0%)	1/10 (10%)	2/21 (10%)	0/22 (0%)
First incidence (days)	702	610	729 (T)	—
Poly-3 test	P=0.129N	P=0.477	P=0.668N	P=0.236N
Testes: Adenoma				
Overall rate	32/50 (64%)	19/50 (38%)	28/50 (56%)	26/50 (52%)
Adjusted rate	74.4%	48.6%	63.6%	62.4%
Terminal rate	11/14 (79%)	8/10 (80%)	18/21 (86%)	17/22 (77%)
First incidence (days)	561	542	499	465
Poly-3 test	P=0.306N	P=0.007N	P=0.180N	P=0.153N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	2/50 (4%)	5/50 (10%)	7/49 (14%)
Adjusted rate	15.2%	5.5%	11.9%	17.8%
Terminal rate	2/14 (14%)	1/10 (10%)	3/21 (14%)	2/22 (9%)
First incidence (days)	595	625	568	465
Poly-3 test	P=0.281	P=0.154N	P=0.452N	P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	2/50 (4%)	5/50 (10%)	7/49 (14%)
Adjusted rate	15.2%	5.5%	11.9%	17.8%
Terminal rate	2/14 (14%)	1/10 (10%)	3/21 (14%)	2/22 (9%)
First incidence (days)	595	625	568	465
Poly-3 test	P=0.281	P=0.154N	P=0.452N	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rate	23/50 (46%)	14/50 (28%)	13/50 (26%)	18/50 (36%)
Adjusted rate	52.4%	35.5%	29.5%	41.7%
Terminal rate	6/14 (43%)	3/10 (30%)	4/21 (19%)	4/22 (18%)
First incidence (days)	394	554	499	379
Poly-3 test	P=0.223N	P=0.083N	P=0.021N	P=0.211N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	46/50 (92%)	48/50 (96%)	45/50 (90%)
Adjusted rate	99.5%	95.9%	97.2%	95.2%
Terminal rate	14/14 (100%)	10/10 (100%)	20/21 (95%)	21/22 (96%)
First incidence (days)	479	463	471	431
Poly-3 test	P=0.188N	P=0.241N	P=0.459N	P=0.206N
All Organs: Malignant Neoplasms				
Overall rate	32/50 (64%)	23/50 (46%)	19/50 (38%)	22/50 (44%)
Adjusted rate	68.2%	53.3%	42.1%	48.8%
Terminal rate	8/14 (57%)	3/10 (30%)	6/21 (29%)	5/22 (23%)
First incidence (days)	101	463	499	379
Poly-3 test	P=0.034N	P=0.096N	P=0.007N	P=0.041N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	49/50 (98%)	47/50 (94%)
Adjusted rate	100.0%	99.3%	98.0%	96.4%
Terminal rate	14/14 (100%)	10/10 (100%)	20/21 (95%)	21/22 (95%)
First incidence (days)	101	463	471	379
Poly-3 test	P=0.107N	P=0.972N	P=0.500N	P=0.264N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreatic islets, pituitary gland, preputial gland, skin, testis, 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 are the P values 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 negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	31	31	25	22
Natural deaths	5	9	4	6
Survivors				
Terminal sacrifice	14	10	21	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)		3 (6%)	3 (6%)
Ulcer				1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(49)
Parasite metazoan	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Ulcer				1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation, acute	1 (2%)			
Parasite metazoan		1 (2%)		
Ulcer	1 (2%)	1 (2%)		1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Ulcer	3 (6%)			1 (2%)
Intestine small, jejunum	(50)	(46)	(48)	(48)
Diverticulum	1 (2%)			
Ulcer	1 (2%)			
Muscularis, inflammation, chronic			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	15 (30%)	5 (10%)	1 (2%)	2 (4%)
Clear cell focus	1 (2%)		3 (6%)	2 (4%)
Degeneration, cystic	2 (4%)	2 (4%)	5 (10%)	2 (4%)
Degeneration, fatty	6 (12%)	5 (10%)	9 (18%)	7 (14%)
Eosinophilic focus	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Hepatodiaphragmatic nodule	6 (12%)	1 (2%)	8 (16%)	4 (8%)
Mixed cell focus	1 (2%)			1 (2%)
Necrosis	2 (4%)			1 (2%)
Bile duct, hyperplasia	1 (2%)			
Centrilobular, degeneration	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Centrilobular, necrosis		1 (2%)	1 (2%)	
Midzonal, vacuolization cytoplasmic				1 (2%)
Sinusoid, congestion		1 (2%)		
Mesentery	(7)	(4)	(8)	(3)
Hemorrhage	1 (14%)			
Artery, inflammation, chronic			1 (13%)	
Artery, thrombosis	2 (29%)			
Fat, necrosis	4 (57%)	3 (75%)	4 (50%)	3 (100%)
Oral mucosa	(7)	(2)	(2)	
Inflammation, suppurative	4 (57%)	1 (50%)		
Gingival, inflammation, suppurative	2 (29%)		2 (100%)	

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	23 (46%)	18 (36%)	26 (52%)	24 (48%)
Artery, inflammation, chronic active	1 (2%)	1 (2%)		
Artery, thrombosis	1 (2%)		1 (2%)	
Duct, atrophy			1 (2%)	
Salivary glands	(50)	(49)	(50)	(50)
Inflammation, chronic			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Inflammation, chronic	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Mineralization	1 (2%)	1 (2%)		
Ulcer	7 (14%)	8 (16%)	9 (18%)	10 (20%)
Epithelium, hyperplasia		1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Mineralization	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Ulcer	7 (14%)	4 (8%)	5 (10%)	4 (8%)
Tongue			(1)	
Inflammation, suppurative			1 (100%)	
Cardiovascular System				
Blood vessel	(4)	(3)		(1)
Mineralization	4 (100%)	3 (100%)		
Heart	(50)	(50)	(50)	(50)
Degeneration, fatty				1 (2%)
Atrium, thrombosis	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Myocardium, degeneration	41 (82%)	41 (82%)	44 (88%)	45 (90%)
Myocardium, mineralization	1 (2%)	1 (2%)	1 (2%)	
Valve, degeneration		1 (2%)		
Valve, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia	16 (32%)	15 (30%)	15 (30%)	12 (24%)
Hypertrophy			2 (4%)	
Necrosis	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Degeneration, cystic		2 (4%)		
Hyperplasia	11 (22%)	9 (18%)	15 (30%)	8 (16%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	4 (8%)	5 (10%)	4 (8%)
Parathyroid gland	(46)	(49)	(48)	(47)
Hyperplasia	2 (4%)	9 (18%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(49)
Cyst	1 (2%)			
Infiltration cellular, mononuclear cell				1 (2%)
Pigmentation, hemosiderin				1 (2%)
Pars distalis, degeneration, cystic	2 (4%)		2 (4%)	2 (4%)
Pars distalis, hyperplasia	4 (8%)	8 (16%)	7 (14%)	8 (16%)
Pars distalis, hypoplasia		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(49)
Cyst	1 (2%)			1 (2%)
Bilateral, follicular cell, cyst			1 (2%)	
C-cell, hyperplasia	33 (66%)	37 (74%)	42 (84%)	33 (67%)
Follicular cell, cyst		2 (4%)		2 (4%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Arteriole, inflammation, chronic	1 (2%)			
Preputial gland	(50)	(50)	(49)	(50)
Hyperplasia		3 (6%)	1 (2%)	2 (4%)
Inflammation, granulomatous	2 (4%)		5 (10%)	3 (6%)
Inflammation, suppurative		1 (2%)		
Prostate	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	
Inflammation, chronic active	2 (4%)			
Inflammation, suppurative	2 (4%)	6 (12%)	3 (6%)	4 (8%)
Necrosis	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy				2 (4%)
Fibrosis			1 (2%)	
Mineralization		1 (2%)		
Necrosis	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	16 (32%)	10 (20%)	11 (22%)	9 (18%)
Interstitial cell, hyperplasia	2 (4%)	1 (2%)		2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Hyperplasia	10 (20%)	4 (8%)	7 (14%)	9 (18%)
Lymph node	(4)	(4)	(5)	(2)
Mediastinal, ectasia				1 (50%)
Mediastinal, hematopoietic cell proliferation	1 (25%)			
Renal, infiltration cellular, plasma cell			1 (20%)	
Lymph node, mandibular	(49)	(48)	(50)	(49)
Atrophy	1 (2%)			
Erythrophagocytosis		1 (2%)		
Hyperplasia, lymphoid			1 (2%)	
Inflammation, acute	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Ectasia	2 (4%)		1 (2%)	1 (2%)
Erythrophagocytosis		1 (2%)		
Hematopoietic cell proliferation	1 (2%)			
Necrosis	1 (2%)			

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	3 (6%)	
Fibrosis	7 (14%)	10 (20%)	9 (18%)	2 (4%)
Hematopoietic cell proliferation		2 (4%)	3 (6%)	1 (2%)
Necrosis	1 (2%)			
Pigmentation, hemosiderin		3 (6%)	1 (2%)	1 (2%)
Lymphoid follicle, atrophy	1 (2%)	2 (4%)		
Lymphoid follicle, necrosis	1 (2%)			
Thymus	(47)	(48)	(48)	(47)
Atrophy	1 (2%)			
Artery, inflammation, chronic	1 (2%)			
Epithelial cell, hyperplasia		1 (2%)		
Integumentary System				
Mammary gland	(46)	(48)	(45)	(42)
Hyperplasia, cystic	5 (11%)	5 (10%)	5 (11%)	1 (2%)
Duct, dilatation			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Inflammation, suppurative				1 (2%)
Dermis, skin, site of application, fibrosis			1 (2%)	1 (2%)
Epidermis, skin, site of application, acanthosis		2 (4%)	4 (8%)	10 (20%)
Epidermis, skin, site of application, degeneration				2 (4%)
Epidermis, skin, site of application, erosion			1 (2%)	
Epidermis, skin, site of application, exudate		3 (6%)	2 (4%)	7 (14%)
Epidermis, skin, site of application, hyperkeratosis		3 (6%)	5 (10%)	11 (22%)
Skin, site of application, ulcer				2 (4%)
Subcutaneous tissue, inflammation, focal, suppurative			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Fibrous osteodystrophy	3 (6%)	4 (8%)	4 (8%)	
Vertebra, hyperostosis				1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Degeneration				1 (2%)
Choroid plexus, thrombosis	1 (2%)			
Medulla, demyelination, focal			1 (2%)	
Medulla, necrosis, focal			2 (4%)	
Spinal cord	(2)		(1)	(1)
Gliosis				1 (100%)
Neuron, degeneration	1 (50%)			

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	16 mg/kg	32 mg/kg	64 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	3 (6%)		
Hemorrhage, focal		1 (2%)		
Inflammation, acute	1 (2%)			
Inflammation, granulomatous	5 (10%)		2 (4%)	2 (4%)
Mineralization	3 (6%)	1 (2%)		
Alveolar epithelium, hyperplasia		5 (10%)	2 (4%)	2 (4%)
Bronchus, infiltration cellular, mononuclear cell				1 (2%)
Bronchus, infiltration cellular, polymorphonuclear				1 (2%)
Interstitium, inflammation, chronic		3 (6%)	1 (2%)	2 (4%)
Nose	(50)	(50)	(50)	(49)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative	2 (4%)	5 (10%)	4 (8%)	9 (18%)
Glands, hyperplasia	1 (2%)			
Special Senses System				
Eye		(2)	(2)	(2)
Cataract		1 (50%)	2 (100%)	
Degeneration		1 (50%)		
Lens, cataract				2 (100%)
Harderian gland	(3)			
Inflammation, acute	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet				1 (2%)
Cyst	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Hydronephrosis		1 (2%)		
Infarct	2 (4%)			
Inflammation, acute	1 (2%)			
Nephropathy	48 (96%)	48 (96%)	50 (100%)	48 (96%)
Urinary bladder	(48)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Inflammation, chronic	1 (2%)			
Ulcer				1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DERMAL STUDY OF DIETHANOLAMINE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	16	12	13
Natural deaths	14	5	9	13
Survivors				
Terminal sacrifice	25	29	29	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(49)
Intestine large, cecum	(50)	(49)	(50)	(49)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Intestine small, jejunum	(48)	(49)	(49)	(46)
Intestine small, ileum	(49)	(49)	(48)	(47)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma				1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)		
Mesentery	(4)	(7)	(6)	(5)
Yolk sac carcinoma, metastatic, ovary				1 (20%)
Oral mucosa	(2)	(2)		(1)
Squamous cell carcinoma		1 (50%)		1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Adrenal medulla	(49)	(50)	(49)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Pheochromocytoma benign		1 (2%)	2 (4%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)	
Carcinoma				1 (2%)
Pituitary gland	(49)	(50)	(50)	(50)
Pars distalis, adenoma	25 (51%)	27 (54%)	30 (60%)	33 (66%)
Pars distalis, adenoma, multiple	2 (4%)	4 (8%)	1 (2%)	1 (2%)
Pars distalis, carcinoma	2 (4%)			
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	8 (16%)	8 (16%)	6 (12%)	5 (10%)
C-cell, carcinoma		1 (2%)		2 (4%)
Follicular cell, carcinoma		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(49)	(47)
Adenoma	4 (8%)	5 (10%)	2 (4%)	
Adenoma, multiple		1 (2%)		
Ovary	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Yolk sac carcinoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Polyp stromal	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Sarcoma stromal	1 (2%)		1 (2%)	1 (2%)
Yolk sac carcinoma, metastatic, ovary				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(1)	(3)	(3)	(3)
Inguinal, yolk sac carcinoma, metastatic, ovary				1 (33%)
Mediastinal, yolk sac carcinoma, metastatic, ovary				1 (33%)
Lymph node, mandibular	(50)	(49)	(50)	(48)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Thymus	(49)	(49)	(47)	(48)
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Adenoma		1 (2%)		
Carcinoma			1 (2%)	
Carcinoma, multiple				1 (2%)
Fibroadenoma	13 (26%)	6 (12%)	9 (18%)	4 (8%)
Fibroadenoma, multiple	1 (2%)	2 (4%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Fibrosarcoma	1 (2%)			
Schwannoma malignant		1 (2%)		
Squamous cell papilloma		1 (2%)		
Trichoepithelioma		1 (2%)		
Conjunctiva, schwannoma malignant		1 (2%)		
Skin, site of application, keratoacanthoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
Osteosarcoma				1 (2%)
Skeletal muscle				(1)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Nervous System				
Brain	(50)	(49)	(50)	(50)
Astrocytoma malignant	1 (2%)			
Carcinoma, metastatic, pituitary gland	1 (2%)			
Medulla, carcinoma, metastatic, pituitary gland	1 (2%)			
Spinal cord				(1)
Glioma malignant				1 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)			
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, thyroid gland				1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa				1 (2%)
Yolk sac carcinoma, metastatic, ovary				1 (2%)
Special Senses System				
Zymbal's gland	(2)		(1)	
Carcinoma	2 (100%)		1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Papilloma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	13 (26%)	10 (20%)	13 (26%)
Lymphoma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	42	43	45
Total primary neoplasms	78	81	68	73
Total animals with benign neoplasms	38	39	40	41
Total benign neoplasms	59	63	53	50
Total animals with malignant neoplasms	17	16	15	22
Total malignant neoplasms	19	18	15	23
Total animals with metastatic neoplasms	2			4
Total metastatic neoplasms	2			13

[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 Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	4 3 8	4 6 0	4 8 9	5 0 6	5 2 2	5 3 1	5 7 9	5 8 9	5 9 7	6 0 0	6 0 6	6 2 2	6 3 2	6 3 8	6 4 8	6 5 0	6 5 2	6 5 3	6 5 8	6 6 6	6 7 1	6 7 8	6 9 7	7 0 1	7 2 9
Carcass ID Number	2 4 2	2 3 9	2 2 2	2 4 4	2 3 5	2 2 3	2 0 4	2 4 1	2 0 9	2 0 2	2 2 0	2 4 0	2 2 9	2 2 7	2 4 3	2 4 6	2 2 8	2 2 6	2 1 4	2 4 9	2 3 2	2 0 1	2 1 5	2 5 0	2 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery				+																			+		
Oral mucosa																									+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X				X	X								X	X	X	X	X	X	X	X		
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma													X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X									X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma stromal																									

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 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 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	
Carcass ID Number	2 0 0 3	2 0 0 6	2 0 0 7	2 0 0 8	2 0 1 6	2 0 1 8	2 0 2 1	2 0 2 5	2 0 3 0	2 0 3 3	2 0 3 4	2 0 3 6	2 0 4 5	2 0 4 7	2 0 5	2 1 1 0	2 1 1 1	2 1 1 2	2 1 1 7	2 1 1 9	2 2 2 4	2 3 1	2 3 3 7	2 3 3 8	2 4 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									1
Mesentery																			+		+					4
Oral mucosa								+																		2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue												+														1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X		X	X			X	X		X	X				X			X	X		X		25
Pars distalis, adenoma, multiple									X										X							2
Pars distalis, carcinoma	X																									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X	X					X						X		X	X							8
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X							X							X				X							4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X																		X					X		3
Sarcoma stromal																				X						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	4 3 8	4 6 0	4 8 9	5 0 6	5 2 2	5 3 1	5 7 9	5 8 9	5 9 7	6 0 0	6 0 6	6 2 2	6 3 2	6 3 8	6 4 8	6 5 0	6 5 2	6 5 3	6 5 8	6 6 6	6 7 1	6 7 8	6 9 7	7 0 1	7 2 9
Carcass ID Number	2 4 2	2 3 9	2 2 2	2 4 4	2 3 5	2 2 3	2 0 4	2 4 1	2 0 9	2 0 2	2 2 0	2 4 0	2 2 9	2 2 7	2 4 3	2 4 6	2 2 8	2 2 6	2 1 4	2 4 9	2 3 2	2 0 1	2 1 5	2 5 0	2 1 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X				X	X		X			
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, pituitary gland																									
Medulla, carcinoma, metastatic, pituitary gland													X												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Zymbal's gland					+		+																		
Carcinoma					X		X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X				X	X		X	X								X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 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 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	
Carcass ID Number	2 0 0 3	2 0 0 6	2 0 0 7	2 0 0 8	2 0 1 6	2 0 1 8	2 0 2 1	2 0 2 5	2 0 3 0	2 0 3 3	2 0 3 4	2 0 3 6	2 0 4 5	2 0 4 7	2 0 5	2 0 1 0	2 0 1 1	2 0 1 2	2 0 1 7	2 0 1 9	2 0 2 4	2 0 3 1	2 0 3 7	2 0 3 8	2 0 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X	X	X					X	X	X								X			X		X	13
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant										X																1
Carcinoma, metastatic, pituitary gland	X																									1
Medulla, carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				2
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+																		2
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X						X		X																11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 8 mg/kg

Number of Days on Study	3 2 3	4 9 2	5 4 1	5 4 4	5 5 6	5 8 9	5 9 7	6 3 8	6 4 1	6 5 5	6 6 6	6 8 1	6 8 9	6 9 9	7 0 2	7 0 3	7 0 3	7 0 3	7 0 4	7 2 2	7 2 4	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 7	2 9 0	2 8 0	2 6 4	2 7 7	2 5 7	2 9 8	2 5 9	2 9 1	2 6 1	2 9 9	2 8 2	2 9 3	2 6 8	2 6 0	2 7 1	2 7 3	2 9 4	2 7 0	3 0 0	2 8 8	2 5 3	2 5 4	2 5 5	2 5 6
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X			
Mesentery										+	+	+						+	+		+		+	
Oral mucosa																								
Squamous cell carcinoma																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X			X		X	X		X	X	X		X		X	X		X				X
Pars distalis, adenoma, multiple																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								X	
C-cell, adenoma							X														X				
C-cell, carcinoma																									
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X												X	X								
Adenoma, multiple																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Vagina					+						+														

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 8 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	731	
Carcass ID Number	26262	26266	26267	26269	26272	26274	26275	26283	26286	26287	26295	26296	26301	26512	26515	26518	26563	26565	26576	26578	26579	26581	26584	26585	26589	26592	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																											1
Mesentery																											7
Oral mucosa		+					+																				2
Squamous cell carcinoma		X																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X								1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X		X		X	X			X	X	X	X		X	X		X	X				X		27
Pars distalis, adenoma, multiple							X									X							X				4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																											1
C-cell, adenoma		X		X					X				X							X	X						8
C-cell, carcinoma																								X			1
Follicular cell, carcinoma																											1
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X		X																					5
Adenoma, multiple																								X			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal						X																					1
Vagina																											2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 8 mg/kg

Number of Days on Study	3 2 3	4 9 2	5 4 1	5 4 4	5 5 6	5 8 9	5 9 7	6 3 8	6 4 1	6 5 5	6 6 6	6 8 1	6 8 9	6 9 9	7 0 2	7 0 3	7 0 3	7 0 3	7 0 4	7 2 2	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 7	2 9 0	2 8 0	2 6 4	2 7 7	2 5 7	2 9 8	2 5 9	2 9 1	2 6 1	2 9 9	2 8 2	2 9 3	2 6 8	2 6 0	2 7 1	2 7 3	2 9 4	2 7 0	3 0 0	2 8 8	2 5 3	2 5 4	2 5 5	2 5 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+		+	+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Fibroadenoma								X							X							X		X	
Fibroadenoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Squamous cell papilloma																						X			
Trichoepithelioma																									
Conjunctiva, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura											+														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland			+																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X			X	X			X	X	X	X	X	X				X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 8 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	731	
Carcass ID Number	26202	26606	26707	26909	27202	27404	27505	28303	28806	28707	29505	29606	25101	25202	25808	26303	26505	27606	27808	27909	28101	28404	28505	28909	29202	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibroadenoma								X																	X	6
Fibroadenoma, multiple				X																						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant					X																					1
Squamous cell papilloma																										1
Trichoepithelioma								X																		1
Conjunctiva, schwannoma malignant									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma					X																					1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																							X			13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	3 5 1	3 6 5	4 3 4	4 9 0	5 6 1	5 7 9	5 9 1	6 0 6	6 1 9	6 3 4	6 4 8	6 5 6	6 6 5	6 7 7	6 7 9	6 9 2	6 9 4	6 9 5	6 9 7	7 1 9	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 4 0	3 1 0	3 2 5	3 1 7	3 1 1	3 2 0	3 4 2	3 4 5	3 3 3	3 1 4	3 3 5	3 1 3	3 3 7	3 3 2	3 4 1	3 2 2	3 0 3	3 0 5	3 1 5	3 0 8	3 3 8	3 0 1	3 0 0	3 0 0	3 0 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+	+			+		+			+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	+	+	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X	X	X		X	X	X	X	X	X			X	X	X			
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X							X							X						X	X
General Body System																									
Peritoneum														+											
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma					X																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X																							
Sarcoma stromal																					X				
Vagina														+											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																+		+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 16 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 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	7 3 1	
Carcass ID Number	3 0 0 9	3 1 3 6	3 3 4	3 3 6	3 3 9	3 4 7	3 4 8	3 4 9	3 5 0	3 0 7	3 1 2	3 1 8	3 1 9	3 2 1	3 2 3	3 2 4	3 2 6	3 2 7	3 2 8	3 2 9	3 3 0	3 3 1	3 4 3	3 4 4	3 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+																								6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue														+												1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign								X																		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X		X	X		X	X			X		X	X		X	X	X		X	X	X	X	30
Pars distalis, adenoma, multiple					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X											6
General Body System																										
Peritoneum																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1
Sarcoma stromal																										1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																				+						3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 16 mg/kg

Number of Days on Study	3 5 1	3 6 5	4 3 4	4 9 0	5 6 1	5 7 9	5 9 1	6 0 6	6 1 9	6 3 4	6 4 8	6 5 6	6 6 5	6 7 7	6 7 9	6 9 2	6 9 4	6 9 5	6 9 7	7 1 9	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 4 0	3 1 0	3 2 5	3 1 7	3 1 1	3 2 0	3 4 2	3 4 5	3 3 3	3 1 4	3 3 5	3 1 3	3 3 7	3 3 2	3 4 1	3 2 2	3 0 3	3 0 5	3 1 5	3 0 8	3 3 8	3 0 1	3 0 0	3 0 0	3 0 6
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X												
Fibroadenoma								X				X		X			X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application, keratoacanthoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Zymbal's gland																						+			
Carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X		X		X					X		X	X						
Lymphoma malignant			X																						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 16 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 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	7 3 1	
Carcass ID Number	3 0 9	3 1 6	3 3 4	3 3 6	3 3 9	3 4 7	3 4 8	3 4 9	3 5 0	3 0 7	3 1 2	3 1 8	3 1 9	3 2 1	3 2 3	3 2 4	3 2 6	3 2 7	3 2 8	3 2 9	3 3 0	3 3 1	3 4 3	3 4 4	3 4 6	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Fibroadenoma		X						X										X		X					X	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application, keratoacanthoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X							X											X						10
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	3 9 5	4 3 0	4 6 5	4 8 6	4 9 0	5 1 5	5 5 9	5 6 5	5 7 2	5 8 4	5 8 9	6 0 9	6 2 1	6 2 9	6 4 2	6 4 6	6 5 6	6 6 8	6 6 9	7 5	7 9 9	7 0 0	7 0 3	7 0 6	7 1 7
Carcass ID Number	3 7 6	3 6 8	3 8 6	3 5 5	3 9 0	3 5 9	3 7 0	3 5 2	3 7 1	3 9 1	3 8 9	3 8 5	3 7 3	3 6 3	3 5 6	3 9 9	3 8 1	3 8 7	3 5 8	3 6 1	3 6 5	3 8 0	3 9 6	3 6 0	3 9 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	M	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery						+				+				+								+			
Yolk sac carcinoma, metastatic, ovary						X																			
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel																		+					+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Osteosarcoma, metastatic, bone																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X		X	X		X		X	X	X	X	X	X		X		X	X		X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																			
C-cell, carcinoma			X																						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Yolk sac carcinoma						X																			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	728	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	35313	35501	36202	36609	37404	37707	38202	38404	38808	38903	39004	40005	40454	35707	36404	36606	36707	37202	37505	37808	37901	38303	39202	39505	39808	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							1
Mesentery																	+									5
Yolk sac carcinoma, metastatic, ovary																										1
Oral mucosa															+											1
Squamous cell carcinoma															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue								+																		1
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Osteosarcoma, metastatic, bone	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone	X																									1
Pheochromocytoma benign					X												X									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																					X					1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X	X	X	X	X	X	X	X	X	X		X	X				X	X	X			33
Pars distalis, adenoma, multiple																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X									X			X						X				5
C-cell, carcinoma											X															2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone	X																									1
Yolk sac carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	3 9 5	4 3 0	4 6 5	4 8 6	4 9 0	5 1 5	5 5 9	5 6 5	5 7 2	5 8 4	5 8 9	6 0 9	6 2 1	6 2 9	6 4 2	6 4 6	6 5 6	6 6 8	6 6 9	6 7 5	6 9 9	7 0 0	7 0 3	7 0 6	7 1 7
Carcass ID Number	3 7 6	3 6 8	3 8 6	3 5 5	3 9 0	3 5 9	3 7 0	3 5 2	3 7 1	3 9 1	3 8 9	3 8 5	3 7 3	3 6 3	3 5 6	3 9 9	3 8 1	3 8 7	3 5 8	3 6 1	3 6 5	3 8 0	3 9 6	3 6 0	3 9 7
Genital System (continued)																									
Oviduct																	+								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X																								
Sarcoma stromal																								X	
Yolk sac carcinoma, metastatic, ovary						X																			
Vagina																	+								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+															+				
Inguinal, yolk sac carcinoma, metastatic, ovary						X																			
Mediastinal, yolk sac carcinoma, metastatic, ovary						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple																									
Fibroadenoma																									
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland			X																						
Osteosarcoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve													+												
Spinal cord													+												
Glioma malignant													X												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland			X																						
Osteosarcoma, metastatic, bone																									
Squamous cell carcinoma, metastatic, oral mucosa																									
Yolk sac carcinoma, metastatic, ovary						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	728	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	35 3	35 1	36 2	36 9	37 4	37 7	38 2	38 4	38 8	38 8	39 3	39 4	40 0	40 4	35 4	35 7	36 4	36 6	36 7	37 2	37 5	37 8	37 9	38 3	39 2	39 5	39 8	Total Tissues/ Tumors
Genital System (continued)																												
Oviduct																												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X																							2
Sarcoma stromal																												1
Yolk sac carcinoma, metastatic, ovary																												1
Vagina																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											+	3
Inguinal, yolk sac carcinoma, metastatic, ovary																												1
Mediastinal, yolk sac carcinoma, metastatic, ovary																												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Thymoma benign																X												1
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, multiple						X																						1
Fibroadenoma	X												X				X					X						4
Fibroadenoma, multiple															X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																												1
Osteosarcoma	X																											1
Skeletal muscle																							+					1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																												1
Spinal cord																												1
Glioma malignant																												1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																												1
Osteosarcoma, metastatic, bone	X																											1
Squamous cell carcinoma, metastatic, oral mucosa																X												1
Yolk sac carcinoma, metastatic, ovary																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	3 9 5	4 3 0	4 6 5	4 8 6	4 9 0	5 1 5	5 5 9	5 6 5	5 7 2	5 8 4	5 8 9	6 0 9	6 2 1	6 2 9	6 4 2	6 4 6	6 5 6	6 6 8	6 6 9	6 7 5	6 9 9	7 0 0	7 0 3	7 0 6	7 1 7
Carcass ID Number	3 7 6	3 6 8	3 8 6	3 5 5	3 9 0	3 5 9	3 7 0	3 5 2	3 7 1	3 9 1	3 8 9	3 8 5	3 7 3	3 6 3	3 5 6	3 9 9	3 8 1	3 8 7	3 5 8	3 6 1	3 6 5	3 8 0	3 9 6	3 6 0	3 9 7
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X						X				X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethanolamine: 32 mg/kg

Number of Days on Study	728	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	35 3	55 1	66 2	66 9	70 4	70 7	70 2	70 4	70 8	70 3	70 4	70 0	70 4	70 7	70 4	70 6	70 6	70 7	70 2	70 5	70 7	70 8	70 9	70 3	70 2	70 5	70 8	Total Tissues/ Tumors
Special Senses System																												
Eye																		+									+	2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone	X																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X									X			X	X				X	X					X	13

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Clitoral Gland: Adenoma				
Overall rate[a]	4/50 (8%)	6/50 (12%)	2/49 (4%)	0/47 (0%)
Adjusted rate[b]	10.0%	13.5%	4.8%	0.0%
Terminal rate[c]	4/25 (16%)	3/29 (10%)	1/29 (3%)	0/22 (0%)
First incidence (days)	730 (T)	544	561	—[e]
Poly-3 test[d]	P=0.025N	P=0.432	P=0.316N	P=0.068N
Mammary Gland: Fibroadenoma				
Overall rate	14/50 (28%)	8/50 (16%)	9/50 (18%)	5/50 (10%)
Adjusted rate	33.9%	18.2%	20.8%	12.6%
Terminal rate	9/25 (36%)	5/29 (17%)	5/29 (17%)	4/24 (17%)
First incidence (days)	648	638	606	728
Poly-3 test	P=0.027N	P=0.075N	P=0.130N	P=0.019N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	14/50 (28%)	9/50 (18%)	9/50 (18%)	5/50 (10%)
Adjusted rate	33.9%	20.1%	20.8%	12.6%
Terminal rate	9/25 (36%)	5/29 (17%)	5/29 (17%)	4/24 (17%)
First incidence (days)	648	492	606	728
Poly-3 test	P=0.024N	P=0.112N	P=0.130N	P=0.019N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	14/50 (28%)	9/50 (18%)	10/50 (20%)	6/50 (12%)
Adjusted rate	33.9%	20.1%	23.0%	15.1%
Terminal rate	9/25 (36%)	5/29 (17%)	5/29 (17%)	5/24 (21%)
First incidence (days)	648	492	606	728
Poly-3 test	P=0.053N	P=0.112N	P=0.187N	P=0.040N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	27/49 (55%)	31/50 (62%)	31/50 (62%)	34/50 (68%)
Adjusted rate	61.7%	66.5%	68.6%	72.4%
Terminal rate	15/25 (60%)	19/29 (66%)	19/29 (66%)	16/24 (67%)
First incidence (days)	460	492	579	430
Poly-3 test	P=0.158	P=0.395	P=0.314	P=0.184
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	29/49 (59%)	31/50 (62%)	31/50 (62%)	34/50 (68%)
Adjusted rate	65.7%	66.5%	68.6%	72.4%
Terminal rate	16/25 (64%)	19/29 (66%)	19/29 (66%)	16/24 (67%)
First incidence (days)	460	492	579	430
Poly-3 test	P=0.252	P=0.559	P=0.471	P=0.315
Thyroid Gland (C-cell): Adenoma				
Overall rate	8/50 (16%)	9/50 (18%)	6/50 (12%)	5/50 (10%)
Adjusted rate	19.7%	20.5%	13.8%	12.4%
Terminal rate	6/25 (24%)	7/29 (24%)	3/29 (10%)	4/24 (17%)
First incidence (days)	638	597	490	515
Poly-3 test	P=0.173N	P=0.573	P=0.334N	P=0.275N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	10/50 (20%)	6/50 (12%)	7/50 (14%)
Adjusted rate	19.7%	22.7%	13.8%	17.0%
Terminal rate	6/25 (24%)	8/29 (28%)	3/29 (10%)	5/24 (21%)
First incidence (days)	638	597	490	465
Poly-3 test	P=0.331N	P=0.470	P=0.334N	P=0.488N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	7.5%	2.3%	2.3%	4.9%
Terminal rate	3/25 (12%)	1/29 (3%)	0/29 (0%)	1/24 (4%)
First incidence (days)	730 (T)	730 (T)	365	395
Poly-3 test	P=0.482N	P=0.276N	P=0.279N	P=0.495N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	10.0%	2.3%	4.6%	7.4%
Terminal rate	4/25 (16%)	1/29 (3%)	0/29 (0%)	1/24 (4%)
First incidence (days)	730 (T)	730 (T)	365	395
Poly-3 test	P=0.555N	P=0.154N	P=0.304N	P=0.492N
All Organs: Mononuclear Cell Leukemia				
Overall rate	11/50 (22%)	13/50 (26%)	10/50 (20%)	13/50 (26%)
Adjusted rate	25.6%	28.6%	22.6%	30.8%
Terminal rate	3/25 (12%)	3/29 (10%)	3/29 (10%)	7/24 (29%)
First incidence (days)	438	556	579	565
Poly-3 test	P=0.383	P=0.467	P=0.468N	P=0.383
All Organs: Benign Neoplasms				
Overall rate	38/50 (76%)	39/50 (78%)	40/50 (80%)	41/50 (82%)
Adjusted rate	84.2%	82.6%	83.8%	84.4%
Terminal rate	24/25 (96%)	24/29 (83%)	23/29 (79%)	19/24 (79%)
First incidence (days)	460	492	365	395
Poly-3 test	P=0.513	P=0.534N	P=0.598N	P=0.610
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	16/50 (32%)	15/50 (30%)	22/50 (44%)
Adjusted rate	38.3%	35.3%	32.8%	49.9%
Terminal rate	6/25 (24%)	6/29 (21%)	4/29 (14%)	11/24 (46%)
First incidence (days)	438	556	434	465
Poly-3 test	P=0.126	P=0.469N	P=0.373N	P=0.181
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	42/50 (84%)	43/50 (86%)	45/50 (90%)
Adjusted rate	95.3%	87.5%	87.6%	90.8%
Terminal rate	24/25 (96%)	24/29 (83%)	23/29 (79%)	21/24 (88%)
First incidence (days)	438	492	365	395
Poly-3 test	P=0.372N	P=0.138N	P=0.147N	P=0.304N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, thyroid gland, and uterus; 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 are the P values 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 negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Mammary Gland Fibroadenoma in Vehicle Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
Benzethonium Chloride	17/51
Coconut Oil Acid Diethanolamine Condensate	18/50
Diethanolamine	14/50
Lauric Acid Diethanolamine Condensate	11/50
Oleic Acid Diethanolamine Condensate	9/50
Sodium Xylenesulfonate	16/50
Overall Historical Incidence	
Total (%)	85/301 (28.2%)
Mean ± standard deviation	28.2% ± 6.9%
Range	18%-36%

[a] Data as of 10 November 1998

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	16	12	13
Natural deaths	14	5	9	13
Survivors				
Terminal sacrifice	25	29	29	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, necrosis		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(49)
Mineralization				1 (2%)
Parasite metazoan	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Ulcer			1 (2%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Mineralization				1 (2%)
Parasite metazoan	4 (8%)		1 (2%)	
Ulcer			1 (2%)	
Intestine large, cecum	(50)	(49)	(50)	(49)
Parasite metazoan		1 (2%)		
Ulcer		1 (2%)	1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(49)
Mineralization				1 (2%)
Ulcer	1 (2%)			2 (4%)
Intestine small, ileum	(49)	(49)	(48)	(47)
Muscularis, inflammation, chronic active, focal				1 (2%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	40 (80%)	31 (62%)	20 (40%)	7 (14%)
Clear cell focus		3 (6%)	2 (4%)	1 (2%)
Congestion	1 (2%)			
Cyst				2 (4%)
Degeneration, cystic				2 (4%)
Eosinophilic focus	1 (2%)	5 (10%)	2 (4%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)			1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	6 (12%)	6 (12%)	8 (16%)
Mixed cell focus		3 (6%)	6 (12%)	1 (2%)
Necrosis		1 (2%)		
Centrilobular, degeneration		1 (2%)	2 (4%)	
Centrilobular, necrosis	2 (4%)			1 (2%)
Oval cell, hyperplasia		1 (2%)		
Periportal, degeneration				1 (2%)
Portal, fibrosis		1 (2%)		
Serosa, fibrosis			1 (2%)	
Mesentery	(4)	(7)	(6)	(5)
Angiectasis				1 (20%)
Inflammation, chronic			1 (17%)	
Fat, necrosis	4 (100%)	6 (86%)	4 (67%)	3 (60%)

[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 Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Alimentary System (continued)				
Oral mucosa	(2)	(2)		(1)
Gingival, inflammation, suppurative	2 (100%)	1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	
Necrosis	1 (2%)	1 (2%)		
Acinus, atrophy	13 (26%)	21 (42%)	11 (22%)	14 (28%)
Artery, inflammation, chronic active				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Inflammation, chronic active				2 (4%)
Mineralization				1 (2%)
Ulcer	2 (4%)	3 (6%)	5 (10%)	6 (12%)
Epithelium, hyperplasia	1 (2%)		2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Mineralization				2 (4%)
Ulcer	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Tongue	(1)		(1)	(1)
Inflammation, suppurative	1 (100%)		1 (100%)	1 (100%)
Cardiovascular System				
Blood vessel				(2)
Mineralization				2 (100%)
Heart	(50)	(50)	(50)	(50)
Atrium, thrombosis	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Myocardium, degeneration	36 (72%)	33 (66%)	35 (70%)	36 (72%)
Myocardium, mineralization				3 (6%)
Valve, fibrosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	13 (26%)	13 (26%)	11 (22%)	11 (22%)
Hypertrophy	1 (2%)	2 (4%)		2 (4%)
Necrosis, acute			1 (2%)	
Thrombosis			1 (2%)	
Bilateral, hypertrophy				1 (2%)
Adrenal medulla	(49)	(50)	(49)	(50)
Hyperplasia	3 (6%)	10 (20%)	4 (8%)	10 (20%)
Necrosis			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	1 (2%)
Parathyroid gland	(43)	(42)	(42)	(49)
Hyperplasia			1 (2%)	1 (2%)
Pituitary gland	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Cyst		1 (2%)		
Hemorrhage	1 (2%)			
Pars distalis, angiectasis				1 (2%)
Pars distalis, degeneration, cystic	5 (10%)	3 (6%)	2 (4%)	4 (8%)
Pars distalis, hyperplasia	3 (6%)	11 (22%)	12 (24%)	5 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	31 (62%)	33 (66%)	39 (78%)	29 (58%)
Follicular cell, cyst		1 (2%)		
Follicular cell, hyperplasia		1 (2%)		
General Body System				
Peritoneum			(1)	
Inflammation, chronic			1 (100%)	
Genital System				
Clitoral gland	(50)	(50)	(49)	(47)
Fibrosis	1 (2%)			
Hyperplasia	4 (8%)	4 (8%)	1 (2%)	2 (4%)
Inflammation, suppurative	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)	(50)
Cyst	4 (8%)	4 (8%)	5 (10%)	8 (16%)
Necrosis		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Necrosis		1 (2%)		
Prolapse		1 (2%)		
Endometrium, hyperplasia, cystic	1 (2%)	1 (2%)	1 (2%)	
Epithelium, hypertrophy		1 (2%)		
Vagina		(2)	(1)	(1)
Infiltration cellular, polymorphonuclear		2 (100%)		
Inflammation, chronic			1 (100%)	
Muscularis, hyperplasia				1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Hyperplasia	2 (4%)	6 (12%)	4 (8%)	5 (10%)
Myelofibrosis	1 (2%)			
Necrosis				1 (2%)
Lymph node, mandibular	(50)	(49)	(50)	(48)
Atrophy	1 (2%)			1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Atrophy	1 (2%)			
Hyperplasia, lymphoid	1 (2%)			
Inflammation, chronic active		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)		3 (6%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Necrosis			1 (2%)	
Capsule, pigmentation, focal, hemosiderin				1 (2%)
Lymphoid follicle, atrophy	2 (4%)	1 (2%)		1 (2%)
Lymphoid follicle, hyperplasia		1 (2%)		
Thymus	(49)	(49)	(47)	(48)
Atrophy	1 (2%)			
Cyst	1 (2%)			
Infiltration cellular, mononuclear cell				1 (2%)
Inflammation, chronic	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	8 mg/kg	16 mg/kg	32 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Epidermis, fibrosis			1 (2%)	
Epidermis, skin, site of application, acanthosis	1 (2%)	1 (2%)	4 (8%)	6 (12%)
Epidermis, skin, site of application, exudate	1 (2%)	7 (14%)	7 (14%)	7 (14%)
Epidermis, skin, site of application, hyperkeratosis	3 (6%)	13 (26%)	23 (46%)	23 (46%)
Skin, site of application, ulcer	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)			2 (4%)
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	5 (10%)	2 (4%)	5 (10%)	5 (10%)
Fibrosis, focal				1 (2%)
Inflammation, granulomatous	3 (6%)	3 (6%)	5 (10%)	9 (18%)
Mineralization				2 (4%)
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Interstitium, inflammation, chronic		2 (4%)	2 (4%)	
Nose	(49)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	
Pleura		(1)		
Inflammation, chronic		1 (100%)		
Special Senses System				
Eye	(2)		(1)	(2)
Cataract	1 (50%)			1 (50%)
Degeneration	1 (50%)			
Anterior chamber, inflammation, suppurative			1 (100%)	
Retina, atrophy				1 (50%)
Harderian gland		(1)		
Inflammation, chronic		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Nephropathy	40 (80%)	47 (94%)	48 (96%)	48 (96%)
Renal tubule, hyperplasia			1 (2%)	
Renal tubule, mineralization			1 (2%)	1 (2%)
Renal tubule, pigmentation, hemosiderin		1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DERMAL STUDY OF DIETHANOLAMINE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund sacrifice	3	1	6	10
Natural deaths	7	6	10	9
Survivors				
Died last week of study		2		
Terminal sacrifice	40	41	34	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(49)	(50)	(50)
Carcinoma			3 (6%)	
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma			2 (4%)	
Hemangiosarcoma, multiple		1 (2%)		
Hepatoblastoma		2 (4%)	8 (16%)	5 (10%)
Hepatocellular carcinoma	10 (20%)	12 (24%)	19 (38%)	17 (34%)
Hepatocellular carcinoma, multiple	2 (4%)	5 (10%)	14 (28%)	17 (34%)
Hepatocellular adenoma	19 (38%)	6 (12%)	2 (4%)	4 (8%)
Hepatocellular adenoma, multiple	12 (24%)	36 (72%)	47 (94%)	41 (82%)
Osteosarcoma, metastatic, bone				1 (2%)
Stomach, forestomach	(50)	(49)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Capsule, adenoma	5 (10%)	8 (16%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Pituitary gland	(48)	(47)	(46)	(43)
Pars intermedia, adenoma	1 (2%)			2 (5%)
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma	4 (8%)	5 (10%)	4 (8%)	2 (4%)
General Body System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Leiomyoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	2 (4%)		2 (4%)	2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Lymph node	(1)	(2)	(1)	
Mediastinal, plasma cell tumor malignant	1 (100%)			
Lymph node, mandibular	(46)	(46)	(44)	(36)
Lymph node, mesenteric	(45)	(43)	(41)	(41)
Plasma cell tumor malignant	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	4 (8%)		
Plasma cell tumor malignant	1 (2%)			
Thymus	(37)	(42)	(39)	(36)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibroma	1 (2%)			1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, lipoma			1 (2%)	
Subcutaneous tissue, pinna, fibroma		1 (2%)		
Subcutaneous tissue, skin, site of application, lymphoma malignant		1 (2%)		
Subcutaneous tissue, skin, site of application, osteosarcoma, metastatic, bone				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Rib, carcinoma, metastatic, islets, pancreatic	1 (2%)			
Vertebra, osteosarcoma				1 (2%)
Skeletal muscle		(2)	(3)	
Hemangiosarcoma		1 (50%)		
Hepatoblastoma, metastatic, liver			1 (33%)	
Nervous System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	13 (26%)	9 (18%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	2 (4%)	1 (2%)	
Alveolar/bronchiolar carcinoma	5 (10%)	1 (2%)	3 (6%)	
Hepatoblastoma, metastatic, liver			2 (4%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	4 (8%)	7 (14%)	4 (8%)
Osteosarcoma, metastatic, bone				1 (2%)
Mediastinum, carcinoma, metastatic, islets, pancreatic	1 (2%)			
Special Senses System				
Harderian gland		(1)	(2)	(1)
Adenoma		1 (100%)	2 (100%)	
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Renal tubule, adenoma	1 (2%)	4 (8%)	4 (8%)	6 (12%)
Renal tubule, adenoma, multiple			2 (4%)	
Renal tubule, carcinoma	2 (4%)	1 (2%)		2 (4%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Lymphoma malignant		1 (2%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	49	50	49
Total primary neoplasms	85	106	128	109
Total animals with benign neoplasms	38	45	49	45
Total benign neoplasms	57	77	76	64
Total animals with malignant neoplasms	21	22	38	35
Total malignant neoplasms	28	29	52	45
Total animals with metastatic neoplasms	4	4	9	8
Total metastatic neoplasms	6	4	10	10

[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 C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	4 1 1	4 7 3	4 8 5	5 9 3	5 9 6	6 1 1	6 4 9	6 7 4	6 7 8	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 9	0 1 2	0 4 7	0 1 0	0 0 4	0 4 9	0 4 2	0 0 8	0 3 4	0 2 1	0 0 1	0 0 7	0 1 4	0 1 6	0 2 0	0 2 2	0 2 7	0 2 8	0 3 1	0 3 3	0 3 6	0 3 9	0 4 3	0 4 6	0 4 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X	X		X		X								X			X						
Hepatocellular carcinoma, multiple							X			X															
Hepatocellular adenoma	X	X		X								X	X	X	X				X	X			X	X	
Hepatocellular adenoma, multiple																	X				X				
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth														+						+					
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					X		X		
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X																				

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 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 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	
Carcass ID Number	0 0 0 2	0 0 2 5	0 0 1 1	0 1 1 5	0 1 1 7	0 1 1 8	0 1 1 9	0 1 2 4	0 2 2 9	0 2 3 0	0 3 3 2	0 3 3 5	0 3 3 8	0 3 4 1	0 4 4 5	0 4 5 3	0 0 0 6	0 1 1 3	0 2 2 3	0 2 2 5	0 2 2 6	0 3 3 7	0 4 4 0	0 4 4 4	0 4 4 4	0 5 5 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma							X		X				X	X													10
Hepatocellular carcinoma, multiple																											2
Hepatocellular adenoma	X		X									X				X			X		X				X	X	19
Hepatocellular adenoma, multiple		X		X	X		X		X		X				X		X	X		X							12
Mesentery									+																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth															+												3
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma	X					X	X									X											5
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	41
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																	X	X									4
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma										X																	1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																		X									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	4 1 1	4 7 3	4 8 5	5 9 3	5 9 6	6 1 1	6 4 9	6 7 4	6 7 8	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 9	0 1 2	0 4 7	0 1 0	0 0 4	0 4 9	0 4 2	0 0 8	0 3 4	0 2 1	0 0 1	0 0 7	0 1 4	0 1 6	0 2 0	0 2 2	0 2 7	0 2 8	0 3 1	0 3 3	0 3 6	0 3 9	0 4 3	0 4 6	0 4 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Lymph node																									
Mediastinal, plasma cell tumor, malignant																									
Lymph node, mandibular	+	+	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+
Plasma cell tumor malignant																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Plasma cell tumor malignant																									
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	M	M	+	+	M	+	M	+	+	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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, carcinoma, metastatic, islets, pancreatic						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X	X								X	X	X
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma									X																
Hepatocellular carcinoma, metastatic, liver							X			X															
Mediastinum, carcinoma, metastatic, islets, pancreatic						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 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 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	
Carcass ID Number	0 0 2	0 0 5	0 1 1	0 1 5	0 1 7	0 1 8	0 1 9	0 2 4	0 2 9	0 3 0	0 3 2	0 3 5	0 3 8	0 4 1	0 4 5	0 0 3	0 0 6	0 1 3	0 2 3	0 2 5	0 2 6	0 3 7	0 4 0	0 4 4	0 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																								+		1
Mediastinal, plasma cell tumor, malignant																								X		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Plasma cell tumor malignant																								X		1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Plasma cell tumor malignant																								X		1
Thymus	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	37
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, fibroma																										1
Subcutaneous tissue, fibrosarcoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, carcinoma, metastatic, islets, pancreatic																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X											X											X		X	9
Alveolar/bronchiolar adenoma multiple					X																					2
Alveolar/bronchiolar carcinoma		X				X						X										X				5
Hepatocellular carcinoma, metastatic, liver														X												3
Mediastinum, carcinoma, metastatic, islets, pancreatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Renal tubule, adenoma																							X			1
Renal tubule, carcinoma				X												X										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	4 9 9	5 7 6	6 4 1	6 7 0	6 9 2	7 0 6	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 9 9	0 0 9 1	0 0 5 5	0 0 9 0	0 0 8 5	0 0 5 2	0 0 6 9	0 0 5 3	0 0 5 4	0 0 6 3	0 0 6 5	0 0 7 1	0 0 7 2	0 0 7 4	0 0 7 5	0 0 7 8	0 0 8 3	0 0 8 4	0 0 8 6	0 0 9 3	0 0 9 4	0 0 9 6	0 0 9 7	0 0 9 8	0 1 0 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatoblastoma																									
Hepatocellular carcinoma							X				X			X		X		X							
Hepatocellular carcinoma, multiple		X			X	X																		X	
Hepatocellular adenoma								X				X		X											
Hepatocellular adenoma, multiple			X	X					X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+						+								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Follicular cell, adenoma																		X							
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	00551	00556	00557	00561	00564	00566	00568	00570	00573	00576	00577	00581	00582	00587	00588	00589	00595	00758	00759	00760	00762	00767	00779	00780	00792	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																					X					1
Hepatoblastoma					X															X					2
Hepatocellular carcinoma			X					X		X	X				X			X			X				12
Hepatocellular carcinoma, multiple							X																			5
Hepatocellular adenoma												X								X			X		6
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X		X		X		X	36
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										2
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Capsule, adenoma														X		X	X	X			X		X		X	8
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	41
Pituitary gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma				X		X				X															X	5
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	4 9 9	5 7 6	6 4 1	6 7 0	6 9 2	7 0 6	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 9 9	0 9 1	0 5 5	0 9 0	0 8 5	0 5 2	0 6 9	0 5 3	0 5 4	0 6 3	0 6 5	0 7 1	0 7 2	0 7 4	0 7 5	0 7 8	0 8 3	0 8 4	0 8 6	0 9 3	0 9 4	0 9 6	0 9 7	0 9 8	1 0 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node																								+	
Lymph node, mandibular	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X		X																						
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
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, pinna, fibroma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X	X	X			X			X			X						X	X			
Alveolar/bronchiolar adenoma, multiple																X									
Alveolar/bronchiolar carcinoma																								X	
Hepatocellular carcinoma, metastatic, liver		X			X		X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																						+			
Adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma					X																				
Renal tubule, carcinoma																				X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 40 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 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	
Carcass ID Number	0 5 1	0 5 6	0 5 7	0 6 1	0 6 4	0 6 6	0 6 8	0 7 0	0 7 3	0 7 6	0 7 7	0 8 1	0 8 2	0 8 7	0 8 8	0 8 9	0 9 5	0 5 8	0 5 9	0 6 0	0 6 2	0 6 7	0 7 9	0 8 0	0 9 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				1
Lymph node							+																			2
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	M	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X														X				4
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	+	+	42
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, pinna, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+													+					2
Hemangiosarcoma								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X										X		X			X				13
Alveolar/bronchiolar adenoma, multiple				X																						2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver			X																							4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma					X			X											X							4
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant							X																			1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	4 4 5	5 5 6	5 5 8	5 8 3	5 9 9	6 3 1	6 3 3	6 4 1	6 5 4	6 6 7	6 8 1	6 8 5	6 9 9	7 0 1	7 1 5	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 2 6	1 2 4	1 3 5	1 0 2	1 1 3	1 2 3	1 4 7	1 2 0	1 2 9	1 3 4	1 2 1	1 3 9	1 4 1	1 2 5	1 1 4	1 1 0	1 0 7	1 1 1	1 1 2	1 1 5	1 1 6	1 1 7	1 2 8	1 4 2	1 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X					X																
Hepatoblastoma							X			X				X		X									
Hepatocellular carcinoma	X	X	X									X	X	X	X			X		X	X				
Hepatocellular carcinoma, multiple				X	X		X	X		X	X						X					X	X		
Hepatocellular adenoma		X														X									
Hepatocellular adenoma, multiple	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X									X						X
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	7 2 9	7 2 9	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 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	
Carcass ID Number	1 4 9	1 5 0	1 0 5	1 0 6	1 0 8	1 1 8	1 1 9	1 2 2	1 3 0	1 3 1	1 3 2	1 3 3	1 3 6	1 3 7	1 3 8	1 4 6	1 0 1	1 0 3	1 0 4	1 0 9	1 2 7	1 4 0	1 4 3	1 4 4	1 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X								X						3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma						X		X						X		X										8
Hepatocellular carcinoma	X					X		X							X		X	X		X	X	X				19
Hepatocellular carcinoma, multiple														X		X			X					X	X	14
Hepatocellular adenoma																										2
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	47
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	M	+	+	M	+	+	M	+	41
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								4
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma	X																X									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	4 4 5	5 5 6	5 5 8	5 8 3	5 9 9	6 3 1	6 3 3	6 4 1	6 5 4	6 6 7	6 8 1	6 8 5	6 9 9	7 0 1	7 1 5	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 2 6	1 2 4	1 3 5	1 0 2	1 1 3	1 2 3	1 4 7	1 2 0	1 2 9	1 3 4	1 2 1	1 3 9	1 4 1	1 2 5	1 1 4	1 1 0	1 0 7	1 1 1	1 1 2	1 1 5	1 1 6	1 1 7	1 2 8	1 4 2	1 4 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																	X								
Subcutaneous tissue, hemangiosarcoma									X																
Subcutaneous tissue, lipoma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Hepatoblastoma, metastatic, liver							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X	X	X								X			X	X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																		X							
Hepatoblastoma, metastatic, liver							X									X									
Hepatocellular carcinoma, metastatic, liver			X										X							X			X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland			+																						
Adenoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma									X		X														
Renal tubule, adenoma, multiple										X															X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	7 2 9	7 2 9	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 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	
Carcass ID Number	1 4 9	1 5 0	1 0 5	1 0 6	1 0 8	1 1 8	1 1 9	1 2 2	1 3 0	1 3 1	1 3 2	1 3 3	1 3 6	1 3 7	1 3 8	1 4 6	1 0 1	1 0 3	1 0 4	1 0 9	1 2 7	1 4 0	1 4 3	1 4 4	1 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																				+						1
Lymph node, mandibular	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	44
Lymph node, mesenteric	+	+	+	+	M	M	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	39
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, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+								+							3
Hepatoblastoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X	X						X								9
Alveolar/bronchiolar adenoma, multiple														X												1
Alveolar/bronchiolar carcinoma				X		X																				3
Hepatoblastoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, liver																X		X	X							7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland											+															2
Adenoma											X															2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X				X																				4
Renal tubule, adenoma, multiple																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	230	386	446	540	598	605	606	634	660	674	684	696	700	706	716	717	719	719	719	723	729	729	729	729	729
Carcass ID Number	189	167	190	172	160	200	585	494	252	299	292	269	270	282	286	279	262	273	287	278	251	253	255	256	261
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma											X			X	X										
Hepatocellular carcinoma			X									X		X	X		X	X						X	
Hepatocellular carcinoma, multiple				X			X	X		X	X		X						X	X					
Hepatocellular adenoma										X		X							X						
Hepatocellular adenoma, multiple		X		X	X	X	X	X	X		X			X	X	X	X	X		X	X	X	X	X	X
Osteosarcoma, metastatic, bone																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					X		X		
General Body System																									
Tissue NOS																		+							
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																							X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	16303	16606	16808	17606	18101	18303	18404	19101	15707	15909	16404	16505	17101	17404	17505	17707	18000	18903	19808	15404	15808	18808	19505	19606	19707	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	M	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M	+	M	M	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																	X							X		5
Hepatocellular carcinoma		X		X	X				X		X	X		X						X		X			X	17
Hepatocellular carcinoma, multiple	X		X										X		X	X	X	X					X			17
Hepatocellular adenoma				X																						4
Hepatocellular adenoma, multiple	X	X	X		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	41
Osteosarcoma, metastatic, bone																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma		X																					X			2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Pars intermedia, adenoma								X												X						2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																		X								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	230	238	446	450	598	605	606	603	606	607	604	608	609	700	700	706	711	711	719	719	719	723	729	729	729	729
Carcass ID Number	189	167	190	172	160	200	185	194	252	299	292	269	270	282	286	279	262	273	287	278	251	253	255	256	261
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	M	M	M	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	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	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma									X																	
Subcutaneous tissue, hemangiosarcoma																										
Subcutaneous tissue, skin, site of application, osteosarcoma, metastatic, bone																		X								
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma																		X								
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																								
Spinal cord		+																								
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Hepatoblastoma, metastatic, liver											X				X											
Hepatocellular carcinoma, metastatic, liver			X									X									X					
Osteosarcoma, metastatic, bone																		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland																										
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma				X					X		X					X										
Renal tubule, carcinoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	16633	16636	16638	17606	18101	18303	18404	19101	15707	15909	16404	16605	17101	17404	17505	17707	18004	19303	19808	20454	15588	18809	19505	19609	19707	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	M	+	M	M	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+	M	+	M	+	36
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, fibroma																										1
Subcutaneous tissue, hemangiosarcoma													X													1
Subcutaneous tissue, skin, site of application, osteosarcoma, metastatic, bone																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X									X						X				X						4
Hepatoblastoma, metastatic, liver																								X		3
Hepatocellular carcinoma, metastatic, liver													X													4
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland													+													1
Carcinoma													X													1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																	X			X						6
Renal tubule, carcinoma					X					X																2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																									X	1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	5/50 (10%)	9/50 (18%)	1/50 (2%)	2/50 (4%)
Adjusted rate[b]	10.9%	18.7%	2.2%	4.6%
Terminal rate[c]	4/40 (10%)	9/43 (21%)	1/34 (3%)	2/30 (7%)
First incidence (days)	678	729 (T)	729 (T)	729 (T)
Poly-3 test[d]	P=0.051N	P=0.219	P=0.106N	P=0.234N
Kidney (Renal Tubule): Adenoma (Single Section)				
Overall rate	1/50 (2%)	4/50 (8%)	6/50 (12%)	6/50 (12%)
Adjusted rate	2.2%	8.3%	13.1%	13.3%
Terminal rate	1/40 (3%)	3/43 (7%)	3/34 (9%)	2/30 (7%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.049	P=0.196	P=0.056	P=0.053
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Section)				
Overall rate	3/50 (6%)	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted rate	6.6%	10.4%	13.1%	17.8%
Terminal rate	3/40 (8%)	4/43 (9%)	3/34 (9%)	4/30 (13%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.064	P=0.386	P=0.242	P=0.093
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	1/50 (2%)	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted rate	2.2%	12.5%	17.5%	15.5%
Terminal rate	1/40 (3%)	5/43 (12%)	5/34 (15%)	3/30 (10%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.046	P=0.065	P=0.016	P=0.028
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	3/50 (6%)	7/50 (14%)	8/50 (16%)	9/50 (18%)
Adjusted rate	6.6%	14.5%	17.5%	20.0%
Terminal rate	3/40 (8%)	6/43 (14%)	5/34 (15%)	5/30 (17%)
First incidence (days)	729 (T)	692	654	540
Poly-3 test	P=0.056	P=0.180	P=0.098	P=0.055
Liver: Hepatocellular Adenoma				
Overall rate	31/50 (62%)	42/50 (84%)	49/50 (98%)	45/50 (90%)
Adjusted rate	65.0%	86.5%	98.0%	93.5%
Terminal rate	28/40 (70%)	40/43 (93%)	33/34 (97%)	28/30 (93%)
First incidence (days)	411	641	445	386
Poly-3 test	P<0.001	P=0.009	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	17/50 (34%)	33/50 (66%)	34/50 (68%)
Adjusted rate	25.1%	34.9%	66.9%	72.3%
Terminal rate	6/40 (15%)	13/43 (30%)	20/34 (59%)	20/30 (67%)
First incidence (days)	485	576	445	446
Poly-3 test	P<0.001	P=0.206	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	39/50 (78%)	47/50 (94%)	50/50 (100%)	49/50 (98%)
Adjusted rate	79.0%	95.3%	100.0%	99.9%
Terminal rate	31/40 (78%)	41/43 (95%)	34/34 (100%)	30/30 (100%)
First incidence (days)	411	576	445	386
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	2/50 (4%)	8/50 (16%)	5/50 (10%)
Adjusted rate	0.0%	4.2%	17.5%	11.3%
Terminal rate	0/40 (0%)	2/43 (5%)	4/34 (12%)	2/30 (7%)
First incidence (days)	—[e]	729 (T)	633	684
Poly-3 test	P=0.018	P=0.249	P=0.004	P=0.028
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	18/50 (36%)	34/50 (68%)	34/50 (68%)
Adjusted rate	25.1%	36.9%	68.9%	72.3%
Terminal rate	6/40 (15%)	14/43 (33%)	20/34 (59%)	20/30 (67%)
First incidence (days)	485	576	445	446
Poly-3 test	P<0.001	P=0.151	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	39/50 (78%)	47/50 (94%)	50/50 (100%)	49/50 (98%)
Adjusted rate	79.0%	95.3%	100.0%	99.9%
Terminal rate	31/40 (78%)	41/43 (95%)	34/34 (100%)	30/30 (100%)
First incidence (days)	411	576	445	386
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	11/50 (22%)	15/50 (30%)	10/50 (20%)	4/50 (8%)
Adjusted rate	24.1%	30.9%	21.8%	9.1%
Terminal rate	11/40 (28%)	12/43 (28%)	7/34 (21%)	4/30 (13%)
First incidence (days)	729 (T)	670	641	729 (T)
Poly-3 test	P=0.020N	P=0.304	P=0.496N	P=0.051N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	10.9%	2.1%	6.7%	0.0%
Terminal rate	4/40 (10%)	1/43 (2%)	3/34 (9%)	0/30 (0%)
First incidence (days)	678	729 (T)	729 (T)	—
Poly-3 test	P=0.042N	P=0.091N	P=0.367N	P=0.034N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	16/50 (32%)	12/50 (24%)	4/50 (8%)
Adjusted rate	32.7%	33.0%	26.2%	9.1%
Terminal rate	14/40 (35%)	13/43 (30%)	9/34 (27%)	4/30 (13%)
First incidence (days)	678	670	641	729 (T)
Poly-3 test	P=0.003N	P=0.574	P=0.324N	P=0.005N
Small Intestine (Jejunum): Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	6.6%	0.0%
Terminal rate	0/40 (0%)	0/43 (0%)	2/34 (6%)	0/30 (0%)
First incidence (days)	—	—	631	—
Poly-3 test	P=0.505	—[f]	P=0.117	—
Spleen: Hemangiosarcoma				
Overall rate	1/50 (2%)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.2%	8.2%	0.0%	0.0%
Terminal rate	0/40 (0%)	2/43 (5%)	0/34 (0%)	0/30 (0%)
First incidence (days)	678	499	—	—
Poly-3 test	P=0.127N	P=0.200	P=0.504N	P=0.509N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	5/49 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	8.8%	10.6%	8.8%	4.6%
Terminal rate	4/40 (10%)	5/42 (12%)	3/34 (9%)	2/30 (7%)
First incidence (days)	729 (T)	729 (T)	667	729 (T)
Poly-3 test	P=0.243N	P=0.518	P=0.638	P=0.355N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.3%	8.2%	6.5%	2.3%
Terminal rate	0/40 (0%)	2/43 (5%)	0/34 (0%)	1/30 (3%)
First incidence (days)	674	499	583	729 (T)
Poly-3 test	P=0.320N	P=0.366	P=0.500	P=0.516N
All Organs: Benign Neoplasms				
Overall rate	38/50 (76%)	45/50 (90%)	49/50 (98%)	45/50 (90%)
Adjusted rate	78.5%	92.2%	98.0%	93.5%
Terminal rate	32/40 (80%)	41/43 (95%)	33/34 (97%)	28/30 (93%)
First incidence (days)	411	641	445	386
Poly-3 test	P=0.012	P=0.044	P=0.002	P=0.028
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	22/50 (44%)	38/50 (76%)	35/50 (70%)
Adjusted rate	43.8%	44.2%	76.0%	74.5%
Terminal rate	14/40 (35%)	16/43 (37%)	22/34 (65%)	21/30 (70%)
First incidence (days)	485	499	445	446
Poly-3 test	P<0.001	P=0.563	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Adjusted rate	92.0%	98.0%	100.0%	99.9%
Terminal rate	36/40 (90%)	42/43 (98%)	34/34 (100%)	30/30 (100%)
First incidence (days)	411	499	445	386
Poly-3 test	P=0.019	P=0.180	P=0.061	P=0.065

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, spleen, 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 are the P values 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 negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE C4a
Historical Incidence of Liver Neoplasms in Vehicle Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratories				
Benzethonium Chloride	24/50	10/50	0/50	29/50
Coconut Oil Acid Diethanolamine Condensate	22/50	12/50	1/50	29/50
Diethanolamine	31/50	12/50	0/50	39/50
Lauric Acid Diethanolamine Condensate	19/50	11/50	0/50	28/50
Oleic Acid Diethanolamine Condensate	22/49	9/49	0/49	29/49
Overall Historical Incidence				
Total (%)	118/249 (47.4%)	54/249 (21.7%)	1/249 (0.4%)	154/249 (61.8%)
Mean ± standard deviation	47.4% ± 8.9%	21.7% ± 2.5%	0.4% ± 0.9%	61.8% ± 9.1%
Range	38%-62%	18%-24%	0%-2%	56%-78%

[a] Data as of 3 November 1998. Vehicle controls from the sodium xylenesulfonate study were excluded because liver neoplasms were associated with hepatitis due to *Helicobacter hepaticus* infection.

TABLE C4b
Historical Incidence of Renal Tubule Neoplasms in Vehicle Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Benzethonium Chloride	0/50	0/50	0/50
Coconut Oil Acid Diethanolamine Condensate	1/50	0/50	1/50
Diethanolamine	1/50	2/50	3/50
Lauric Acid Diethanolamine Condensate	0/50	0/50	0/50
Oleic Acid Diethanolamine Condensate	0/49	0/49	0/49
Sodium Xylenesulfonate	0/50	0/50	0/50
Overall Historical Incidence			
Total (%)	2/299 (0.7%)	2/299 (0.7%)	4/299 (1.3%)
Mean ± standard deviation	0.7% ± 1.0%	0.7% ± 1.6%	1.3% ± 2.4%
Range	0%-2%	0%-4%	0%-6%

[a] Data as of 3 November 1998

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	3	1	6	10
Natural deaths	7	6	10	9
Survivors				
Died last week of study		2		
Terminal sacrifice	40	41	34	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(50)	(49)	(50)	(50)
Lymphoid tissue, hyperplasia, lymphoid		1 (2%)		
Lymphoid tissue, inflammation, chronic active			1 (2%)	
Intestine small, duodenum	(50)	(49)	(49)	(50)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	2 (4%)	1 (2%)		
Clear cell focus	4 (8%)	7 (14%)	2 (4%)	2 (4%)
Clear cell focus, multiple	1 (2%)			
Eosinophilic focus	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Eosinophilic focus, multiple				1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hematopoietic cell proliferation, diffuse		1 (2%)		
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)		
Inflammation, suppurative			1 (2%)	
Necrosis	2 (4%)			
Syncytial alteration		28 (56%)	38 (76%)	23 (46%)
Thrombosis		1 (2%)	1 (2%)	
Centrilobular, cytoplasmic alteration	1 (2%)	17 (34%)	17 (34%)	12 (24%)
Mesentery	(1)			
Fat, inflammation, chronic	1 (100%)			
Pancreas	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Acinus, atrophy	2 (4%)	2 (4%)		1 (2%)
Acinus, cytoplasmic alteration	1 (2%)		1 (2%)	3 (6%)
Salivary glands	(50)	(50)	(50)	(50)
Duct, cytoplasmic alteration	1 (2%)	2 (4%)	8 (16%)	23 (46%)
Stomach, forestomach	(50)	(49)	(50)	(50)
Hyperplasia, focal, squamous	1 (2%)	4 (8%)	4 (8%)	2 (4%)
Stomach, glandular	(50)	(49)	(50)	(50)
Necrosis		1 (2%)	1 (2%)	
Pigmentation			3 (6%)	
Epithelium, hyperplasia, focal		1 (2%)		2 (4%)
Tooth	(3)	(2)		
Developmental malformation	1 (33%)	2 (100%)		
Peridontal tissue, inflammation, chronic active	2 (67%)			

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(49)
Adventitia, inflammation, chronic				1 (2%)
Heart	(50)	(50)	(50)	(50)
Atrium, thrombosis				6 (12%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)	3 (6%)
Hypertrophy, diffuse	1 (2%)			
Hypertrophy, focal	6 (12%)	8 (16%)	4 (8%)	7 (14%)
Vacuolization cytoplasmic, focal			1 (2%)	
Capsule, hyperplasia	2 (4%)	6 (12%)	5 (10%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)			
Parathyroid gland	(41)	(41)	(41)	(43)
Cyst		1 (2%)		
Pituitary gland	(48)	(47)	(46)	(43)
Craniopharyngeal duct, pars distalis, cyst	1 (2%)			
Pars distalis, cyst	2 (4%)	1 (2%)	1 (2%)	3 (7%)
Pars distalis, hyperplasia	2 (4%)			
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, hyperplasia	18 (36%)	22 (45%)	30 (60%)	42 (84%)
General Body System				
Tissue NOS				(1)
Pelvic, abscess				1 (100%)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm				1 (2%)
Preputial gland	(50)	(50)	(50)	(49)
Cyst	16 (32%)	12 (24%)	20 (40%)	12 (24%)
Inflammation, chronic active	3 (6%)	5 (10%)	1 (2%)	3 (6%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Inflammation, diffuse, suppurative		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, diffuse, suppurative		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myeloid cell, depletion cellular			1 (2%)	
Lymph node	(1)	(2)	(1)	
Hyperplasia, lymphoid		1 (50%)		
Lymph node, mandibular	(46)	(46)	(44)	(36)
Necrosis		3 (7%)	2 (5%)	2 (6%)
Lymph node, mesenteric	(45)	(43)	(41)	(41)
Angiectasis	1 (2%)			
Congestion	2 (4%)		1 (2%)	
Inflammation, suppurative			1 (2%)	
Necrosis		4 (9%)	1 (2%)	6 (15%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	13 (26%)	22 (44%)	29 (58%)	32 (64%)
Hyperplasia, lymphoid		1 (2%)		
Thrombosis		1 (2%)		
Lymphoid follicle, necrosis	1 (2%)			
Red pulp, depletion cellular	1 (2%)			
Thymus	(37)	(42)	(39)	(36)
Atrophy	8 (22%)	8 (19%)	18 (46%)	17 (47%)
Cyst		1 (2%)		
Necrosis	2 (5%)	1 (2%)	3 (8%)	2 (6%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis				1 (2%)
Dermis, fibrosis				1 (2%)
Skin, site of application, acanthosis			2 (4%)	4 (8%)
Skin, site of application, exudate				3 (6%)
Skin, site of application, hyperkeratosis		13 (26%)	10 (20%)	17 (34%)
Skin, site of application, inflammation, chronic				1 (2%)
Skin, site of application, ulcer	1 (2%)		1 (2%)	
Subcutaneous tissue, angiectasis	1 (2%)			
Subcutaneous tissue, edema				1 (2%)
Subcutaneous tissue, fibrosis			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, diffuse, granulomatous			1 (2%)	
Inflammation, suppurative			1 (2%)	
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Alveolus, infiltration cellular, histiocyte				1 (2%)
Special Senses System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis	1 (2%)			
Infiltration cellular, lymphocyte	2 (4%)		1 (2%)	
Inflammation, chronic, diffuse			1 (2%)	
Nephropathy	45 (90%)	47 (94%)	45 (90%)	48 (96%)
Cortex, cyst		5 (10%)	2 (4%)	
Cortex, infarct		1 (2%)		
Glomerulus, dilatation, diffuse	1 (2%)		1 (2%)	1 (2%)
Glomerulus, dilatation, focal	22 (44%)	39 (78%)	39 (78%)	32 (64%)
Pelvis, inflammation, suppurative		1 (2%)		
Renal tubule, dilatation		1 (2%)		
Renal tubule, hyperplasia, focal	1 (2%)	2 (4%)		3 (6%)
Renal tubule, mineralization	38 (76%)	45 (90%)	38 (76%)	41 (82%)
Renal tubule, pigmentation, hemosiderin		1 (2%)	2 (4%)	1 (2%)
Renal tubule, vacuolization cytoplasmic				1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DERMAL STUDY OF DIETHANOLAMINE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	4	8	9	13
Natural deaths	2	9	8	14
Survivors				
Died last week of study				1
Terminal sacrifice	44	33	33	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(49)
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Hemangioma	1 (2%)			
Hepatoblastoma		2 (4%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	5 (10%)	13 (26%)	17 (34%)	16 (32%)
Hepatocellular carcinoma, multiple		6 (12%)	21 (42%)	26 (52%)
Hepatocellular adenoma	16 (32%)	7 (14%)	2 (4%)	3 (6%)
Hepatocellular adenoma, multiple	16 (32%)	43 (86%)	46 (92%)	45 (90%)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Mesentery	(4)	(5)	(1)	(2)
Fat, fibrosarcoma		1 (20%)		
Pancreas	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(49)
Squamous cell papilloma	1 (2%)		1 (2%)	
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Capsule, adenoma				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma		1 (2%)		
Pituitary gland	(50)	(50)	(47)	(44)
Pars distalis, adenoma	7 (14%)		3 (6%)	1 (2%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Follicular cell, adenoma	3 (6%)	8 (16%)	7 (14%)	3 (6%)
Follicular cell, adenoma, multiple	1 (2%)	1 (2%)		
General Body System				
Tissue NOS			(1)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Genital System				
Clitoral gland	(46)	(48)	(46)	(43)
Ovary	(49)	(50)	(49)	(49)
Cystadenoma	2 (4%)			
Granulosa-theca tumor benign			1 (2%)	
Hemangioma	3 (6%)			1 (2%)
Teratoma benign			1 (2%)	
Teratoma malignant				1 (2%)
Periovarian tissue, histiocytic sarcoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Polyp stromal	3 (6%)	2 (4%)	2 (4%)	
Cervix, histiocytic sarcoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Mast cell tumor malignant			1 (2%)	
Lymph node	(9)	(2)	(5)	
Inguinal, sarcoma	1 (11%)			
Mediastinal, fibrosarcoma, metastatic, mesentery		1 (50%)		
Renal, fibrous histiocytoma			1 (20%)	
Lymph node, mandibular	(46)	(48)	(46)	(43)
Carcinoma, metastatic, harderian gland		1 (2%)		
Histiocytic sarcoma				2 (5%)
Mast cell tumor malignant			1 (2%)	
Lymph node, mesenteric	(48)	(48)	(44)	(40)
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Histiocytic sarcoma				1 (3%)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)			
Histiocytic sarcoma				2 (4%)
Capsule, fibrosarcoma, metastatic, mesentery		1 (2%)		
Thymus	(48)	(42)	(41)	(36)
Histiocytic sarcoma				1 (3%)
Mast cell tumor malignant			1 (2%)	
Integumentary System				
Mammary gland	(49)	(47)	(47)	(40)
Carcinoma	1 (2%)		2 (4%)	
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		2 (4%)	1 (2%)	
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, sebaceous gland, squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, pinna, fibroma			1 (2%)	
Subcutaneous tissue, skin, site of application, fibrosarcoma		1 (2%)		
Subcutaneous tissue, skin, site of application, sarcoma	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Musculoskeletal System				
Skeletal muscle	(1)	(1)		
Fibrosarcoma, metastatic, skin		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meninges, mast cell tumor malignant			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)	
Carcinoma, metastatic, harderian gland		1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver		3 (6%)	6 (12%)	1 (2%)
Histiocytic sarcoma				1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Mediastinum, fibrosarcoma, metastatic, skin		1 (2%)		
Nose	(50)	(50)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Special Senses System				
Harderian gland	(1)	(2)	(1)	(3)
Adenoma	1 (100%)	1 (50%)	1 (100%)	2 (67%)
Carcinoma		1 (50%)		1 (33%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(49)	(50)	(48)
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)		2 (4%)
Lymphoma malignant	12 (24%)	6 (12%)	11 (22%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	50	50	50
Total primary neoplasms	90	98	128	107
Total animals with benign neoplasms	40	50	49	48
Total benign neoplasms	62	64	68	58
Total animals with malignant neoplasms	22	26	44	44
Total malignant neoplasms	28	34	60	49
Total animals with metastatic neoplasms		8	6	1
Total metastatic neoplasms		15	7	1

[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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 2 8	2 3 0	2 3 2	2 3 8	2 4 0	2 4 1	2 4 2	2 4 3	2 4 5	2 5 0	2 0 2	2 0 7	2 1 0	2 1 1	2 2 0	2 2 1	2 2 2	2 2 4	2 2 9	2 3 5	2 3 6	2 3 7	2 3 9	2 4 6	2 4 8	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
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatocellular carcinoma									X	X																5
Hepatocellular adenoma				X								X			X	X	X		X					X		16
Hepatocellular adenoma, multiple		X				X		X	X		X		X								X		X			16
Histiocytic sarcoma																										1
Mesentery			+																							4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																						X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X					X				X	X											X				7
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X								X							X										3
Follicular cell, adenoma, multiple						X																				1
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma										X								X								2
Hemangioma												X														3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	5 0 8	5 7 6	6 5 9	6 7 4	6 9 2	7 2 9	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	2 1 2	2 2 7	2 3 3	2 2 6	2 0 9	2 4 7	2 1 3	2 1 5	2 1 8	2 1 9	2 3 1	2 3 4	2 4 4	2 4 9	2 0 1	2 0 3	2 0 4	2 0 5	2 0 6	2 0 8	2 1 4	2 1 6	2 1 7	2 2 3	2 2 5
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Polyp stromal										X															
Cervix, histiocytic sarcoma					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+		+		+																	+		
Inguinal, sarcoma																									
Lymph node, mandibular	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sebaceous gland, squamous cell carcinoma	X																								
Subcutaneous tissue, skin, site of application, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma			X																	X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant		X		X		X					X				X					X			X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: Vehicle Control

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 2 8	2 3 0	2 3 2	2 3 8	2 4 0	2 4 1	2 4 2	2 4 3	2 4 5	2 5 0	2 0 2	2 0 7	2 1 0	2 1 1	2 2 0	2 2 1	2 2 2	2 2 4	2 2 9	2 3 5	2 3 6	2 3 7	2 3 9	2 4 6	2 4 8	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Polyp stromal																			X	X						3
Cervix, histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			1
Lymph node			+				+	+								+										9
Inguinal, sarcoma							X																			1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X							X												2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma														X												1
Subcutaneous tissue, sebaceous gland, squamous cell carcinoma																										1
Subcutaneous tissue, skin, site of application, sarcoma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																+										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X						X														X					4
Alveolar/bronchiolar carcinoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																								+		1
Adenoma																								X		1
Lacrimal gland									+																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant		X	X					X													X			X		12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	4 1 8	4 2 1	4 2 3	4 2 4	4 5 8	4 9 1	5 1 4	5 2 6	5 2 7	5 3 4	5 9 9	6 1 0	6 4 9	6 5 5	6 8 9	6 9 1	6 9 6	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	2 8 6	2 6 1	2 7 3	2 8 7	2 6 4	2 9 7	2 8 2	2 6 9	2 8 3	2 7 2	2 5 8	2 5 4	2 6 3	2 6 7	2 9 5	2 9 0	2 7 1	2 5 2	2 6 8	2 9 9	2 9 6	2 6 0	2 6 2	2 7 0	2 7 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery																									
Hepatoblastoma		X																							
Hepatocellular carcinoma			X								X	X		X		X									
Hepatocellular carcinoma, multiple										X							X							X	X
Hepatocellular adenoma		X								X	X						X								
Hepatocellular adenoma, multiple	X		X	X	X	X	X	X	X			X	X	X	X	X		X	X	X	X	X	X	X	X
Histiocytic sarcoma																									
Mesentery								+		+			+								+				
Fat, fibrosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X							
Follicular cell, adenoma, multiple																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery																									
Polyp stromal	X																						X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 7 5	2 8 0	2 8 1	2 8 4	2 8 9	2 9 3	2 9 6	2 9 8	3 0 0	2 5 1	2 5 3	2 5 5	2 5 7	2 5 9	2 6 5	2 6 6	2 7 6	2 7 7	2 7 8	2 7 9	2 8 5	2 8 8	2 9 1	2 9 2	2 9 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																	X									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																	X									1
Hepatoblastoma	X																									2
Hepatocellular carcinoma	X		X		X				X		X	X					X	X								13
Hepatocellular carcinoma, multiple		X																	X							6
Hepatocellular adenoma							X			X				X												7
Hepatocellular adenoma, multiple	X	X	X	X	X	X		X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	43
Histiocytic sarcoma															X											1
Mesentery																	+									5
Fat, fibrosarcoma																	X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma							X			X			X	X	X					X					X	8
Follicular cell, adenoma, multiple			X																							1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, mesentery																	X									1
Polyp stromal																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	4 1 8	4 2 1	4 2 3	4 2 4	4 5 8	4 9 1	5 1 4	5 2 6	5 2 7	5 3 4	5 9 9	6 1 0	6 4 9	6 5 5	6 8 9	6 9 1	6 9 6	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	2 8 6	2 6 1	2 7 3	2 8 7	2 6 4	2 9 7	2 8 2	2 6 9	2 8 3	2 7 2	2 5 8	2 5 4	2 6 3	2 6 7	2 9 5	2 9 0	2 7 1	2 5 2	2 6 8	2 9 9	2 5 6	2 6 0	2 6 2	2 7 0	2 7 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+														
Mediastinal, fibrosarcoma, metastatic, mesentery																									
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland				X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrosarcoma, metastatic, mesentery																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																X									
Subcutaneous tissue, skin, site of application, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Fibrosarcoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma	X																								
Carcinoma, metastatic, harderian gland				X																					
Hepatocellular carcinoma, metastatic, liver			X									X													
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Mediastinum, fibrosarcoma, metastatic, skin																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland				+									+												
Adenoma													X												
Carcinoma				X																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, mesentery																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant											X	X													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 40 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 7 5	2 8 0	2 8 1	2 8 4	2 8 9	2 9 3	2 9 6	2 9 8	3 0 0	2 5 1	2 5 3	2 5 5	2 5 7	2 5 9	2 6 5	2 6 6	2 7 6	2 7 7	2 7 8	2 7 9	2 8 5	2 8 8	2 9 1	2 9 2	2 9 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																	+									2
Mediastinal, fibrosarcoma, metastatic, mesentery																	X									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, mesentery																	X									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrosarcoma, metastatic, mesentery																	X									1
Thymus	M	+	+	+	+	M	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma								X																		2
Subcutaneous tissue, skin, site of application, fibrosarcoma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+																		1
Fibrosarcoma, metastatic, skin								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						1
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																		X								3
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										2
Adenoma																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, mesentery																	X									1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											1
Lymphoma malignant					X					X					X								X			6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	4 7 4	5 3 9	5 4 0	5 5 6	5 6 8	6 0 0	6 1 4	6 1 4	6 2 6	6 3 3	6 3 8	6 8 4	6 8 4	6 9 6	7 1 2	7 2 5	7 3 0	7 3 1	7 1 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2
Carcass ID Number	3 1 9	3 4 8	3 0 6	3 2 5	3 1 0	3 0 3	3 0 5	3 3 1	3 1 4	3 4 2	3 4 9	3 0 9	3 3 5	3 1 6	3 2 2	3 4 3	3 0 8	3 0 4	3 0 7	3 2 0	3 3 8	3 4 3	3 4 6	3 1 1	3 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma			X	X	X			X					X					X	X	X						
Hepatocellular carcinoma, multiple	X	X							X	X		X		X	X							X	X		X
Hepatocellular adenoma		X																							
Hepatocellular adenoma, multiple	X		X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Mesentery																+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma						X															X			X	
General Body System																									
Tissue NOS																+									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign										X															
Teratoma benign															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 1 5	3 2 3	3 2 6	3 2 7	3 3 4	3 3 6	3 3 8	3 4 4	3 4 5	3 4 7	3 4 0	3 0 1	3 0 2	3 1 2	3 1 7	3 1 8	3 2 1	3 2 4	3 2 9	3 3 0	3 3 2	3 3 7	3 3 9	3 4 0	3 4 1	3 5 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
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
Hepatoblastoma																			X								1
Hepatocellular carcinoma			X					X						X	X	X	X					X	X		X		17
Hepatocellular carcinoma, multiple	X	X			X	X	X			X		X						X		X				X		X	21
Hepatocellular adenoma					X																						2
Hepatocellular adenoma, multiple	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Mesentery																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																					X						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	M	M	+		38
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+		47
Pars distalis, adenoma				X												X						X					3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X	X			X																	X				7
General Body System																											
Tissue NOS																											1
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa-theca tumor benign																											1
Teratoma benign																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal														X			X										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	4 7 4	5 3 9	5 4 0	5 5 6	5 6 8	6 0 0	6 1 4	6 1 4	6 2 6	6 3 3	6 3 8	6 8 4	6 8 4	6 9 6	7 1 2	7 2 5	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 2	7 3 2
Carcass ID Number	3 1 9	3 4 8	3 0 6	3 2 5	3 1 0	3 0 3	3 0 5	3 3 1	3 1 4	3 4 2	3 4 9	3 0 9	3 3 5	3 1 6	3 2 2	3 4 3	3 0 8	3 0 4	3 0 7	3 0 0	3 2 2	3 2 8	3 3 3	3 4 6	3 1 1	3 1 3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																										
Lymph node							+									+										
Renal, fibrous histiocytoma																										
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																										
Lymph node, mesenteric	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Mast cell tumor malignant																										
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X														
Subcutaneous tissue, pinna, fibroma																		X								
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, mast cell tumor malignant																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X								
Alveolar/bronchiolar carcinoma													X													
Carcinoma, metastatic, mammary gland									X																	
Hepatocellular carcinoma, metastatic, liver								X	X			X		X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																										
Harderian gland																										
Adenoma																										
Lacrimal gland																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X									X					X	X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 80 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 1 5	3 2 3	3 2 6	3 2 7	3 3 4	3 3 6	3 3 8	3 4 4	3 4 5	3 4 7	3 4 1	3 0 1	3 0 2	3 1 2	3 1 7	3 1 8	3 2 1	3 2 4	3 2 9	3 3 0	3 3 2	3 3 7	3 3 9	3 4 0	3 4 1	3 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																						X				1
Lymph node			+	+			+																			5
Renal, fibrous histiocytoma				X																						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Mast cell tumor malignant																						X				1
Lymph node, mesenteric	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	I	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	41
Mast cell tumor malignant																						X				1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Carcinoma									X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, pinna, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, mast cell tumor malignant																						X				1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Alveolar/bronchiolar carcinoma						X																				2
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver										X				X												6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																						+				1
Harderian gland																						+				1
Adenoma																						X				1
Lacrimal gland																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X		X	X	X	X						X										X		11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	5 2 2	5 8 5	5 9 3	5 9 4	5 9 9	6 0 6	6 0 6	6 0 7	6 0 7	6 1 1	6 3 1	6 4 1	6 5 8	6 7 4	6 8 1	6 9 4	6 9 6	7 0 1	7 0 1	7 0 9	7 1 4	7 1 6	7 1 6	7 1 7	7 2 1
Carcass ID Number	3 6 0	3 8 1	3 9 3	3 9 6	3 9 1	3 7 5	3 9 2	3 7 2	3 8 2	3 5 8	3 5 2	3 9 8	3 8 5	3 7 4	3 6 2	3 9 5	3 8 0	3 7 3	3 8 9	3 8 3	3 5 4	3 5 6	3 7 6	3 5 1	3 8 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma			X	X			X		X			X	X		X	X			X	X	X		X		X
Hepatocellular carcinoma, multiple	X	X				X		X		X	X			X			X	X				X			
Hepatocellular adenoma														X								X			
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X		X	X	X
Histiocytic sarcoma																									
Mesentery						+				+															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Teratoma malignant																						X			
Periovarian tissue, histiocytic sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	7 2 4	7 2 6	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 6 1	3 5 7	3 5 3	3 6 6	3 7 1	3 7 8	3 9 0	3 6 4	3 6 7	3 6 9	3 7 0	3 7 9	3 8 4	3 9 4	3 9 9	4 0 0	3 5 5	3 5 9	3 6 3	3 6 5	3 6 8	3 7 7	3 7 8	3 8 8	3 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																				X						1
Hepatocellular carcinoma							X			X												X				16
Hepatocellular carcinoma, multiple	X		X	X	X	X		X	X		X	X	X				X	X	X		X		X	X		26
Hepatocellular adenoma											X															3
Hepatocellular adenoma, multiple		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Histiocytic sarcoma										X																1
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma										X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma													X													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	M	42
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	44
Pars distalis, adenoma										X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																					X		X		X	3
General Body System																										
None																										
Genital System																										
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	43
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Teratoma malignant																										1
Periovarian tissue, histiocytic sarcoma										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	5 2 2	5 8 5	5 9 3	5 9 4	5 9 9	6 0 6	6 0 6	6 0 7	6 0 7	6 1 1	6 3 1	6 4 1	6 5 8	6 7 4	6 8 1	6 9 4	6 9 6	7 0 1	7 0 1	7 0 9	7 1 4	7 1 6	7 1 6	7 1 7	7 2 1
Carcass ID Number	3 6 0	3 8 1	3 9 3	3 9 6	3 9 1	3 7 5	3 9 2	3 7 2	3 8 2	3 5 8	3 5 2	3 9 8	3 8 5	3 7 4	3 6 2	3 9 5	3 8 0	3 7 3	3 8 9	3 8 3	3 5 4	3 5 6	3 7 6	3 5 1	3 8 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	M	+	+	M	M	M	+	M	M	+	+	M	+	M	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	M	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	M	M	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Harderian gland							+																		
Adenoma																									
Carcinoma							X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant						X																			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethanolamine: 160 mg/kg

Number of Days on Study	7 2 4	7 2 6	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 6 1	3 5 7	3 5 3	3 6 6	3 7 1	3 7 8	3 9 0	3 6 4	3 6 7	3 6 9	3 7 0	3 7 9	3 8 4	3 9 4	3 9 9	4 0 0	3 5 5	3 5 9	3 6 3	3 6 5	3 6 8	3 7 7	3 8 7	3 8 8	3 9 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Histiocytic sarcoma										X				X												2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	40
Histiocytic sarcoma														X												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X				X												2
Thymus	M	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	M	M	36
Histiocytic sarcoma														X												1
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	40
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Hepatocellular carcinoma, metastatic, liver											X															1
Histiocytic sarcoma														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye													+													2
Harderian gland		+											+													3
Adenoma		X											X													2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X				X												2
Lymphoma malignant									X																	2

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Harderian Gland: Adenoma or Carcinoma				
Overall rate[a]	1/50 (2%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate[b]	2.1%	4.8%	2.3%	6.9%
Terminal rate[c]	1/44 (2%)	0/33 (0%)	1/33 (3%)	1/23 (4%)
First incidence (days)	731 (T)	424	731 (T)	606
Poly-3 test[d]	P=0.212	P=0.452	P=0.740	P=0.270
Liver: Hepatocellular Adenoma				
Overall rate	32/50 (64%)	50/50 (100%)	48/50 (96%)	48/50 (96%)
Adjusted rate	66.1%	100.0%	96.4%	96.4%
Terminal rate	30/44 (68%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	5/50 (10%)	19/50 (38%)	38/50 (76%)	42/50 (84%)
Adjusted rate	10.4%	43.4%	77.9%	84.9%
Terminal rate	4/44 (9%)	12/33 (36%)	26/33 (79%)	18/23 (78%)
First incidence (days)	729	423	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	33/50 (66%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	68.2%	100.0%	100.0%	100.0%
Terminal rate	31/44 (71%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	5/50 (10%)	20/50 (40%)	39/50 (78%)	43/50 (86%)
Adjusted rate	10.4%	44.9%	79.9%	86.9%
Terminal rate	4/44 (9%)	12/33 (36%)	27/33 (82%)	19/23 (83%)
First incidence (days)	729	421	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	33/50 (66%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	68.2%	100.0%	100.0%	100.0%
Terminal rate	31/44 (71%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	674	418	474	522
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.3%	2.4%	4.5%	2.3%
Terminal rate	4/44 (9%)	1/33 (3%)	2/33 (6%)	1/23 (4%)
First incidence (days)	731 (T)	731 (T)	731 (T)	731 (T)
Poly-3 test	P=0.169N	P=0.233N	P=0.379N	P=0.215N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	12.4%	4.8%	9.0%	2.3%
Terminal rate	5/44 (11%)	1/33 (3%)	3/33 (9%)	1/23 (4%)
First incidence (days)	659	418	684	731 (T)
Poly-3 test	P=0.075N	P=0.187N	P=0.428N	P=0.078N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Ovary: Hemangioma				
Overall rate	3/49 (6%)	0/50 (0%)	0/49 (0%)	1/49 (2%)
Adjusted rate	6.4%	0.0%	0.0%	2.4%
Terminal rate	3/43 (7%)	0/33 (0%)	0/32 (0%)	0/22 (0%)
First incidence (days)	731 (T)	—[e]	—	721
Poly-3 test	P=0.228N	P=0.147N	P=0.136N	P=0.347N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	0/50 (0%)	3/47 (6%)	1/44 (2%)
Adjusted rate	14.5%	0.0%	7.3%	2.6%
Terminal rate	6/44 (14%)	0/33 (0%)	3/31 (10%)	1/20 (5%)
First incidence (days)	674	—	731 (T)	731 (T)
Poly-3 test	P=0.052N	P=0.015N	P=0.231N	P=0.065N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	7.3%	2.3%	0.0%
Terminal rate	0/44 (0%)	2/33 (6%)	0/33 (0%)	0/23 (0%)
First incidence (days)	—	691	684	—
Poly-3 test	P=0.426N	P=0.093	P=0.483	—[f]
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.1%	7.3%	2.3%	0.0%
Terminal rate	1/44 (2%)	2/33 (6%)	0/33 (0%)	0/23 (0%)
First incidence (days)	731 (T)	691	684	—
Poly-3 test	P=0.237N	P=0.251	P=0.741	P=0.522N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	2.1%	7.3%	4.5%	0.0%
Terminal rate	1/44 (2%)	2/33 (6%)	1/33 (3%)	0/23 (0%)
First incidence (days)	731 (T)	691	684	—
Poly-3 test	P=0.287N	P=0.251	P=0.470	P=0.522N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	9/50 (18%)	7/50 (14%)	3/49 (6%)
Adjusted rate	8.3%	22.0%	15.7%	7.1%
Terminal rate	4/44 (9%)	9/33 (27%)	6/33 (18%)	3/23 (13%)
First incidence (days)	731 (T)	731 (T)	600	731 (T)
Poly-3 test	P=0.355N	P=0.063	P=0.217	P=0.571N
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.2%	4.8%	4.5%	0.0%
Terminal rate	3/44 (7%)	1/33 (3%)	2/33 (6%)	0/23 (0%)
First incidence (days)	731 (T)	418	731 (T)	—
Poly-3 test	P=0.098N	P=0.565N	P=0.541N	P=0.140N
All Organs: Hemangioma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	6.2%	0.0%	0.0%	4.6%
Terminal rate	3/44 (7%)	0/33 (0%)	0/33 (0%)	0/23 (0%)
First incidence (days)	731 (T)	—	—	701
Poly-3 test	P=0.509N	P=0.151N	P=0.136N	P=0.549N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	5/50 (10%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	10.4%	0.0%	0.0%	4.6%
Terminal rate	5/44 (11%)	0/33 (0%)	0/33 (0%)	0/23 (0%)
First incidence (days)	731 (T)	—	—	701
Poly-3 test	P=0.176N	P=0.047N	P=0.039N	P=0.263N
All Organs: Malignant Lymphoma				
Overall rate	12/50 (24%)	6/50 (12%)	11/50 (22%)	2/50 (4%)
Adjusted rate	24.5%	14.4%	24.7%	4.6%
Terminal rate	9/44 (20%)	4/33 (12%)	9/33 (27%)	1/23 (4%)
First incidence (days)	576	599	614	606
Poly-3 test	P=0.015N	P=0.173N	P=0.586	P=0.007N
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	50/50 (100%)	49/50 (98%)	48/50 (96%)
Adjusted rate	82.2%	100.0%	98.3%	96.4%
Terminal rate	37/44 (84%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	659	418	474	522
Poly-3 test	P=0.013	P<0.001	P=0.006	P=0.019
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	26/50 (52%)	44/50 (88%)	44/50 (88%)
Adjusted rate	44.0%	56.3%	89.4%	88.9%
Terminal rate	16/44 (36%)	16/33 (49%)	30/33 (91%)	20/23 (87%)
First incidence (days)	508	418	474	522
Poly-3 test	P<0.001	P=0.158	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	94.0%	100.0%	100.0%	100.0%
Terminal rate	41/44 (93%)	33/33 (100%)	33/33 (100%)	23/23 (100%)
First incidence (days)	508	418	474	522
Poly-3 test	P=0.045	P=0.119	P=0.119	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, ovary, pituitary gland, skin, thyroid gland, and uterus; 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 are the P values 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 negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed

TABLE D4
Historical Incidence of Liver Neoplasms in Vehicle Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratories				
Benzethonium Chloride	20/52	12/52	0/52	27/52
Coconut Oil Acid Diethanolamine Condensate	32/50	3/50	0/50	33/50
Diethanolamine	32/50	5/50	0/50	33/50
Lauric Acid Diethanolamine Condensate	23/50	10/50	0/50	28/50
Oleic Acid Diethanolamine Condensate	26/50	5/50	1/50	28/50
Overall Historical Incidence				
Total (%)	133/252 (52.8%)	35/252 (13.9%)	1/252 (0.4%)	149/252 (59.1%)
Mean ± standard deviation	52.9% ± 11.2%	13.8% ± 7.3%	0.4% ± 0.9%	59.2% ± 6.4%
Range	38%-64%	6%-23%	0%-2%	52%-66%

[a] Data as of 3 November 1998. Vehicle controls from the sodium xylenesulfonate study were excluded because liver neoplasms were associated with hepatitis due to *Helicobacter hepaticus* infection.

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethanolamine[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	4	8	9	13
Natural deaths	2	9	8	14
Survivors				
Died last week of study				1
Terminal sacrifice	44	33	33	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(49)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Clear cell focus		2 (4%)		
Eosinophilic focus	3 (6%)	4 (8%)		
Necrosis	1 (2%)	1 (2%)	1 (2%)	
Syncytial alteration		2 (4%)	17 (34%)	18 (36%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)			
Periportal, Kupffer cell, amyloid deposition	1 (2%)			
Mesentery	(4)	(5)	(1)	(2)
Fat, inflammation, chronic	3 (75%)	4 (80%)		1 (50%)
Pancreas	(50)	(50)	(50)	(49)
Inflammation, granulomatous	1 (2%)			
Acinus, atrophy		2 (4%)		
Acinus, cytoplasmic alteration, focal	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte				1 (2%)
Duct, cytoplasmic alteration	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(49)
Hyperplasia, focal, squamous	1 (2%)	6 (12%)	5 (10%)	
Mineralization, diffuse		1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(49)
Necrosis, focal				3 (6%)
Tooth	(1)			
Developmental malformation	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Atrium, thrombosis			1 (2%)	4 (8%)
Myocardium, degeneration, acute		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Amyloid deposition	1 (2%)			
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Degeneration, diffuse				1 (2%)
Hemorrhage			1 (2%)	4 (8%)
Hypertrophy, diffuse	1 (2%)			
Hypertrophy, focal				1 (2%)
Necrosis		1 (2%)		
Vacuolization cytoplasmic, focal	1 (2%)			
Zona reticularis, pigmentation	1 (2%)			

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia, focal		2 (4%)	1 (2%)	2 (4%)
Pituitary gland	(50)	(50)	(47)	(44)
Pars distalis, cyst	1 (2%)	1 (2%)	2 (4%)	
Pars distalis, hemorrhage, focal		1 (2%)		
Pars distalis, hyperplasia	4 (8%)	4 (8%)	3 (6%)	1 (2%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Follicle, cyst			1 (2%)	1 (2%)
Follicular cell, hyperplasia	18 (36%)	28 (56%)	32 (64%)	39 (80%)
General Body System				
None				
Genital System				
Clitoral gland	(46)	(48)	(46)	(43)
Cyst		1 (2%)		
Ovary	(49)	(50)	(49)	(49)
Atrophy	42 (86%)	35 (70%)	44 (90%)	49 (100%)
Thrombosis	1 (2%)		1 (2%)	1 (2%)
Follicle, cyst	10 (20%)	18 (36%)	12 (24%)	10 (20%)
Periovarian tissue, cyst		1 (2%)	1 (2%)	1 (2%)
Periovarian tissue, inflammation, granulomatous	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Congestion			1 (2%)	
Hyperplasia	1 (2%)			
Infiltration cellular, lymphocyte			1 (2%)	
Thrombosis				1 (2%)
Endometrium, hyperplasia, cystic	45 (90%)	44 (88%)	31 (62%)	25 (50%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myelofibrosis	14 (28%)	19 (38%)	11 (22%)	8 (16%)
Myeloid cell, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Lymph node	(9)	(2)	(5)	
Lumbar, infiltration cellular, plasma cell	1 (11%)			
Mediastinal, hyperplasia, lymphoid	1 (11%)			
Pancreatic, inflammation, granulomatous	1 (11%)			
Lymph node, mandibular	(46)	(48)	(46)	(43)
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, plasma cell				1 (2%)
Necrosis	1 (2%)			3 (7%)
Lymph node, mesenteric	(48)	(48)	(44)	(40)
Congestion			1 (2%)	
Necrosis	2 (4%)	3 (6%)	2 (5%)	7 (18%)
Spleen	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	24 (48%)	31 (62%)	41 (82%)	43 (86%)
Hyperplasia, lymphoid		2 (4%)		1 (2%)
Pigmentation, diffuse, hemosiderin	1 (2%)			
Pigmentation, hemosiderin				1 (2%)
Lymphoid follicle, depletion cellular		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethanolamine

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Hematopoietic System (continued)				
Thymus	(48)	(42)	(41)	(36)
Atrophy	3 (6%)	6 (14%)	8 (20%)	21 (58%)
Hyperplasia, lymphoid	1 (2%)			
Necrosis		6 (14%)	3 (7%)	4 (11%)
Integumentary System				
Mammary gland	(49)	(47)	(47)	(40)
Hyperplasia	1 (2%)		2 (4%)	
Skin	(50)	(50)	(50)	(50)
Skin, site of application, acanthosis		2 (4%)	1 (2%)	2 (4%)
Skin, site of application, exudate		1 (2%)	1 (2%)	3 (6%)
Skin, site of application, hyperkeratosis	1 (2%)	3 (6%)	8 (16%)	16 (32%)
Skin, site of application, ulcer		1 (2%)		
Subcutaneous tissue, edema, diffuse		1 (2%)		
Musculoskeletal System				
Skeletal muscle	(1)	(1)		
Inflammation, granulomatous	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hydrocephalus	1 (2%)			
Cerebrum, cyst epithelial inclusion	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)	1 (2%)
Alveolus, infiltration cellular, histiocyte			2 (4%)	
Special Senses System				
Eye			(1)	(2)
Degeneration				2 (100%)
Cornea, inflammation, chronic active			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Metaplasia, focal, osseous	2 (4%)			
Nephropathy	25 (50%)	24 (48%)	16 (32%)	17 (34%)
Cortex, cyst	1 (2%)		1 (2%)	
Cortex, infarct	1 (2%)			2 (4%)
Glomerulus, amyloid deposition	1 (2%)			
Renal tubule, dilatation			1 (2%)	
Renal tubule, mineralization		4 (8%)	3 (6%)	
Renal tubule, pigmentation		1 (2%)		
Urinary bladder	(50)	(49)	(50)	(48)
Infiltration cellular, lymphocyte			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). Diethanolamine 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 diethanolamine. The high dose was limited by toxicity; 3,333 μg/plate was selected as the high dose. 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.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by Myhr *et al.* (1985). Diethanolamine was supplied as a coded aliquot by Radian Corporation. The high dose of 400 nL/mL was determined by toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with diethanolamine continued for 4 hours, at which time the medium plus diethanolamine was removed and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated with freshly prepared S9 from the livers of Aroclor 1254-induced male Fischer 344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for diethanolamine to be considered

positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Loveday *et al.* (1989). Diethanolamine 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 of at least three doses of diethanolamine; the high dose was limited to 1,500 μg/mL. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with diethanolamine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing diethanolamine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2.5 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 diethanolamine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no diethanolamine. Incubation proceeded for an additional 25.5 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 diethanolamine for 8 hours; Colcemid was added and incubation continued for 2.5 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 diethanolamine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

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.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of a 13-week toxicity study (NTP, 1992), 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 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 up to 10 male and female mice per dose group.

Log transformation of NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analysis. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance with the SAS GLM procedure. The NCE data for each dosed group were compared with the concurrent solvent control group by Student's *t*-test.

RESULTS

Diethanolamine (33 to 3,333 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 when tested with a preincubation protocol in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983; Table E1). No induction of TFT resistance was observed in L5178Y mouse lymphoma cells treated with diethanolamine with or without Aroclor 1254-induced male Fisher 344 rat liver S9 (Table E2). In the assay, an increase in pH was noted at all but one (25 nL/mL) of the concentrations tested. Diethanolamine did not induce SCEs or Abs in cultured CHO cells, with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Loveday *et al.*, 1989; Tables E3 and E4). In the chromosomal aberrations assay, the trial with S9 produced a dose-related increase in the percentage of cells with Abs; however, this increase was not large enough for a positive determination. As with the mouse lymphoma assay, pH increases due to the presence of diethanolamine in the culture medium were noted. Peripheral blood samples taken from male and female mice dermally administered 80 to 1,250 mg diethanolamine/kg body weight in 95% ethanol dermally for 13 weeks showed no increase in the frequency of micronucleated NCEs (Table E5).

TABLE E1
Mutagenicity of Diethanolamine 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	131 ± 6.7	124 ± 3.8	206 ± 7.2	198 ± 4.2	173 ± 16.0	163 ± 5.0
	33	143 ± 4.3	127 ± 6.6	211 ± 7.3	189 ± 7.5	203 ± 6.3	172 ± 14.2
	100	132 ± 5.3	130 ± 3.9	211 ± 12.3	194 ± 6.9	219 ± 11.0	160 ± 4.7
	333	141 ± 5.9	125 ± 6.1	239 ± 6.1	198 ± 15.6	216 ± 7.1	180 ± 13.0
	1,000	144 ± 3.2	121 ± 7.8	233 ± 1.8	178 ± 9.2	228 ± 15.4	153 ± 6.4
	3,333	122 ± 3.0	119 ± 3.7	208 ± 4.7	180 ± 12.9	203 ± 7.9	167 ± 12.9
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Negative
Positive control[c]		527 ± 16.6	365 ± 3.5	808 ± 44.4	651 ± 112.2	442 ± 47.1	365 ± 15.9
TA1535	0	8 ± 1.7	8 ± 0.7	10 ± 1.2	10 ± 0.7	12 ± 2.3	12 ± 0.6
	33	11 ± 2.3	8 ± 1.7	15 ± 0.7	11 ± 2.3	14 ± 2.4	12 ± 1.2
	100	5 ± 0.7	6 ± 0.7	17 ± 2.2	13 ± 2.5	11 ± 2.1	9 ± 1.5
	333	9 ± 2.7	9 ± 0.3	14 ± 3.2	10 ± 1.9	19 ± 1.5	11 ± 4.0
	1,000	8 ± 1.9	8 ± 0.9	18 ± 2.7	13 ± 3.0	15 ± 2.1	12 ± 1.7
	3,333	9 ± 1.8	7 ± 0.9	19 ± 1.8	11 ± 4.7	17 ± 4.1	12 ± 2.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		380 ± 30.1	227 ± 11.8	40 ± 12.1	33 ± 7.7	30 ± 7.0	25 ± 4.4
TA1537	0	9 ± 1.5	8 ± 2.1	10 ± 2.0	8 ± 1.2	11 ± 1.5	9 ± 1.9
	33	7 ± 1.2	4 ± 1.2	10 ± 2.3	7 ± 0.7	14 ± 1.5	8 ± 1.5
	100	6 ± 0.3	5 ± 1.5	8 ± 2.9	6 ± 0.9	12 ± 1.5	8 ± 1.0
	333	4 ± 0.7	3 ± 0.9	9 ± 1.7	7 ± 0.6	14 ± 1.8	5 ± 3.0
	1,000	8 ± 0.3	5 ± 1.5	12 ± 2.2	7 ± 1.2	10 ± 1.2	7 ± 2.1
	3,333	6 ± 0.3	7 ± 2.5	12 ± 1.9	6 ± 1.5	8 ± 0.6	7 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		380 ± 78.5	119 ± 20.5	59 ± 5.5	65 ± 3.2	33 ± 4.1	25 ± 4.4
TA98	0	17 ± 2.5	16 ± 0.7	24 ± 5.0	35 ± 5.8	20 ± 3.8	30 ± 5.2
	33	14 ± 3.0	14 ± 0.9	21 ± 1.5	37 ± 3.1	27 ± 3.5	41 ± 2.9
	100	17 ± 1.5	18 ± 0.9	18 ± 2.6	38 ± 5.8	22 ± 3.7	36 ± 1.8
	333	17 ± 1.5	16 ± 1.7	17 ± 2.5	25 ± 0.3	24 ± 1.7	41 ± 2.6
	1,000	11 ± 2.7	20 ± 4.7	19 ± 0.6	33 ± 3.5	21 ± 2.0	45 ± 6.4
	3,333	15 ± 0.9	18 ± 2.1	20 ± 4.1	33 ± 3.0	20 ± 1.8	31 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		600 ± 94.4	190 ± 1.5	812 ± 54.4	677 ± 103.6	303 ± 10.1	322 ± 54.7

[a] Study was performed at Case Western Reserve University. The detailed protocol and these data are presented by Haworth *et al.* (1983). 0 μg/plate was the solvent control.
[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 E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Diethanolamine[a]

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
S9						
Trial 1						
Ethanol[c]		92	91	66	24	
		75	80	51	23	
		96	108	65	23	
		113	121	84	25	24
Methyl methanesulfonate[d] (μg/mL)	5	55	27	578	352	
		48	42	582	403	
		48	28	472	329	361*
Diethanolamine (nL/mL)	25	53	57	39	24	
		75	70	54	24	
		85	91	49	19	23
	50	93	90	44	16	
		66	92	33	17	
		98	85	47	16	16
	100	70	68	48	23	
		80	62	46	19	
		68	66	53	26	23
	200	66	35	59	30	
		75	42	50	22	
		61	43	31	17	23
	300	47	12	47	33	
		70	14	46	22	27
		Lethal				
	400	Lethal				
		Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Diethanolamine

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
S9						
Trial 2						
Ethanol		95	109	81	28	
		111	102	80	24	
		114	117	34	10	
		75	73	37	16	20
Methyl methanesulfonate (μg/mL)	5	69	57	277	134	
		56	49	390	233	
		59	55	448	252	206*
Diethanolamine (nL/mL)	50[e]	89	91	66	25	
		109	86	87	27	
		100	108	83	28	26
	100	98	96	115	39	
		105	100	127	40	
		110	102	102	31	37*
	150	110	98	108	33	
		108	58	91	28	
		93	96	87	31	31*
	200	117	104	93	26	
		118	89	93	26	
		89	99	88	33	29
	300	96	78	74	26	
		85	64	67	26	
		116	59	81	23	25
	400	98	51	59	20	
		97	38	78	30	
		93	38	65	23	24
	600	Lethal				
		Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Diethanolamine

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Ethanol		80	111	103	43	
		81	114	102	42	
		76	92	117	52	
		62	83	105	56	48
Methylcholanthrene[d]	2.5	58	21	710	412	
(μg/mL)		47	20	622	438	
		50	52	621	413	421*
Diethanolamine	25	58	109	94	54	
(nL/mL)		55	75	82	50	
		70	106	96	46	50
	50[e]	65	90	131	67	
		91	120	122	45	
		66	93	97	49	54
	100	64	91	104	54	
		80	114	130	54	
		74	108	120	54	54
	200	49	96	72	49	
		76	93	130	57	
		60	94	99	55	54
	300	56	86	94	56	
		70	99	92	44	
		73	90	101	46	49
	400	63	67	106	56	
		80	83	115	48	
		53	72	54	34	46
	600	Lethal				
		Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Diethanolamine

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 2						
Ethanol		76	96	120	53	
		85	117	68	27	
		68	95	92	45	
		72	91	83	38	41
Methylcholanthrene	2.5	60	63	651	363	
(μg/mL)		74	61	716	323	
		62	68	482	260	315*
Diethanolamine	100[e]	57	83	60	35	
(nL/mL)		68	67	63	31	33
	200	72	62	66	31	
		62	69	72	39	
		81	78	72	30	33
	300	72	37	77	36	
		67	13	71	35	
		67	27	75	37	36
	400	Lethal				
		Lethal				
		Lethal				

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics. The detailed protocol is presented by Myhr *et al.* (1985).
[b] Mutant fraction = mutant cells/10^6 clonable cells
[c] Solvent control
[d] Positive control
[e] Basic pH shift at this concentration and greater

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Diethanolamine[a]

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
–S9								
Summary: Negative								
Medium[c]		50	1,049	465	0.44	9.3	26.5	
Mitomycin-C[d]	0.002	50	1,044	727	0.69	14.5	26.5	57.10
	0.01	10	207	319	1.54	31.9	26.5	247.66
Diethanolamine	150	50	1,046	459	0.43	9.2	26.5	–1.01
	500[e]	50	1,046	487	0.46	9.7	26.5	5.03
	1,500	50	1,037	469	0.45	9.4	26.5	2.03
					P=0.277[f]			
+S9								
Summary: Negative								
Medium		50	1,006	518	0.51	10.4	25.5	
Cyclophosphamide[d]	0.5	50	1,016	1,053	1.03	21.1	25.5	101.28
	2.5	10	201	592	2.94	59.2	25.5	472.00
Diethanolamine	150	50	1,018	505	0.49	10.1	25.5	–3.66
	500	50	1,011	539	0.53	10.8	25.5	3.54
	1,500[e]	50	1,003	565	0.56	11.3	25.5	9.40
					P=0.038			

[a] Study was performed at Bioassay Systems Corporation. The detailed protocol and these data are presented by Loveday *et al.* (1989). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Alkaline pH at this concentration; for culture with S9, the pH change was noted at the time of washing and addition of fresh medium but had returned to normal by the time of cell harvest.
[f] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Diethanolamine[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
–S9					
Harvest time: 10.5 hours					
Summary: Negative					
Medium[b]		100	1	0.01	1.0
Mitomycin-C[c]	5	100	33	0.33	24.0
Diethanolamine	101	100	1	0.01	1.0
	505	100	0	0.00	0.0
	2,010	100	2	0.02	2.0
					P=0.340[d]
+S9					
Harvest time: 12 hours					
Summary: Negative					
Medium		100	3	0.03	2
Cyclophosphamide[c]	50	100	55	0.55	34
Diethanolamine	303	100	1	0.01	1.0
	1,010[e]	100	2	0.02	2.0
	3,010	100	8	0.08	7.0
					P=0.019

[a] Study was performed at Bioassay Systems Corporation. The detailed protocol and these data are presented by Loveday *et al*. (1989).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[e] Alkaline pH shift at this concentration

TABLE E5
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Dermal Application of Diethanolamine for 13 Weeks[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	NCEs with Micronuclei[b] (%)
Male			
Ethanol[c]		10	0.14 ± 0.02
Diethanolamine	80	10	0.14 ± 0.02
	160	9	0.14 ± 0.01
	320	9	0.11 ± 0.01
	630	10	0.11 ± 0.02
	1,250	8	0.08 ± 0.01
Urethane[d]	0.2%	3	1.87 ± 0.24
Female			
Ethanol		10	0.08 ± 0.01
Diethanolamine	80	10	0.08 ±0.01
	160	10	0.08 ±0.01
	320	10	0.07 ±0.01
	630	10	0.07 ±0.01
	1,250	5	0.07 ±0.01

[a] Study was performed by the United States Department of Agriculture. The detailed protocol is presented by MacGregor *et al.* (1990). NCE=normochromatic erythrocyte
[b] Mean ± standard error; differences from the vehicle control group were not significant by Student's *t*-test
[c] Vehicle control
[d] Positive control. Three male mice were treated with urethane in drinking water; these animals were not part of the 13-week toxicity study (NTP, 1992).

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

PROCUREMENT AND CHARACTERIZATION

Diethanolamine

Diethanolamine was obtained from Kodak Laboratory and Specialty Chemicals (Rochester, NY) in one lot (A16) which was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the diethanolamine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless, viscous liquid, was identified as diethanolamine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure; the infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) and are presented in Figures F1 and F2. The boiling point and density of the chemical were also consistent with a literature reference (*Merck Index*, 1989).

The purity of lot A16 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and gas chromatography. Functional group titration for nonaqueous amines was performed by dissolving the sample in glacial acetic acid and titrating with 0.1 N perchloric acid in glacial acetic acid. The titration was monitored potentiometrically with a pH/mV electrode filled with aqueous 4 M potassium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) chloroform:methanol:concentrated ammonium hydroxide (55:40:5) and 2) methanol:concentrated ammonium hydroxide (90:10). Triethanolamine was used as a reference standard. Plates were visualized with a spray of 0.5% ninhydrin in butanol, followed by heating at 110° C for 10 minutes, and with iodine vapor. Gas chromatography with flame ionization detection (GC/FID) was used with two systems:

A) Tenax GC 60/80 mesh glass column, with a nitrogen carrier gas at a flow rate of 32 mL/minute and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

B) DB-17 capillary fused-silica column, with a helium carrier gas at a flow rate of 20 mL/minute and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for diethanolamine. Karl Fischer water analysis indicated 0.10% ± 0.02% water. Functional group titration indicated a purity of 100.1% ± 0.7%. Analysis by TLC indicated a major spot and one trace impurity by one system and a major spot and two trace impurities by a second system. GC/FID by each of two systems indicated no impurities equal to or greater than 0.1% relative to the major peak. The overall purity of lot A16 was determined to be greater than 99%.

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 lot A16 were determined by Covance Laboratories, Inc. (Madison, WI). For measurement of nonpolar nitrosamines, samples were diluted with high-performance liquid chromatography (HPLC)-grade water and then partitioned three times with dichloromethane:pentane (35:65); samples were vortexed and centrifuged

between each partitioning. The pentane fractions were transferred to a Kuderna-Danish concentrator tube with an attached concentrator flask, and dichloromethane, isooctane, and an ebullator were added. A three-ball Snyder column prewet with dichloromethane was attached to the concentrator tube, and the entire apparatus was placed in a hot water bath until the volume of the solvent was reduced to 4 to 8 mL. The sample was allowed to cool, and the concentrated extract was collected with dichloromethane. The sample was then heated under a stream of nitrogen until the concentration was less than 1 mL; the volume was adjusted to 1.0 mL with isooctane. The samples were then analyzed for nonpolar nitrosamines by gas chromatography with a thermal energy detector, a 10% Carbowax 1540 100/120 WHP in 5% KOH column, and an argon carrier gas at a flow rate of 25 mL/minute. The oven temperature program was 120° C for 4 minutes, then 120° to 180° C at 4° C per minute, with a final hold of 8 minutes at 180° C. No nonpolar nitrosamines were present at concentrations greater than the limit of detection (0.1 ppm).

For determination of the polar nitrosamine N-nitrosodiethanolamine, samples were diluted with distilled water, and 1 N hydrogen chloride was added. The samples were mixed and shaken, then further diluted with distilled water and remixed. Two cation exchange columns were prepared; first the solvent, then 0.05 N hydrogen chloride, then distilled water was drained in the column to the top of the resin bed. The columns were connected in a series with a ChemElut-extraction column. The sample, followed by distilled water, was allowed to drip through the three columns and allowed to be absorbed onto the dry column for 10 minutes. The columns were then rinsed with 10% acetone in ethyl acetate; N-nitrosodiethanolamine was eluted with additional acetone in ethyl acetate, and the samples were concentrated to complete dryness on a rotary evaporator with a hot water bath. The dry column was rinsed with methanol three times, and the collected samples were dried under a stream of nitrogen; 1 mL of methanol was added, and the samples were then analyzed for N-nitrosodiethanolamine by HPLC with a thermal energy detector, an Alltech platinum 5μ CN column, and an isocratic solvent system of isooctane:dichloromethane:methanol (71:18:11). The flow rate was 0.4 mL/minute. No N-nitrosodiethanolamine was present at a concentration greater than the limit of detection (1.0 ppm).

An accelerated stability study was performed by the analytical chemistry laboratory. GC/FID was performed using system A from the purity analyses but with a carrier gas flow rate of 20 mL/minute and an oven temperature program of 230° to 260° C at 10° C/minute with a 1-minute hold at 260° C. This study indicated that diethanolamine was stable as a bulk chemical for 2 weeks when protected from light and stored at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in sealed amber glass containers, in a metal drum, at room temperature. Stability was monitored by the study laboratory using the GC/FID system described for the accelerated stability study. No degradation of the bulk chemical was detected.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY). The purity was monitored by the study laboratory throughout the study by GC/FID. The system used was a 60/80 Carbopack B/1% SP-1000 glass column with a nitrogen carrier gas at a flow rate of 20 mL/minute. The oven temperature program was 80° C for 4 minutes and then 80° to 220° C at 10° C/minute. United States Pharmacopeia ethanol reference standard samples were analyzed concomitantly. Purity of the bulk ethanol ranged from 98.7% to 101.3% that of the reference standard during the studies. No volatile impurities were detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by mixing diethanolamine with 95% ethanol to give the desired concentration (Table F1). The dose formulations were stored at room temperature, protected from light, in amber glass bottles for up to 28 days.

Stability studies of a 0.5 mg/mL formulation were performed by the analytical chemistry laboratory using GC/FID by system A, but with a carrier gas flow rate of 15 mL/minute and an oven temperature of 160° C. The formulation had only small losses of diethanolamine (<5%) when stored at room temperature, protected from light, for up to 28 days; it was stable for 3 hours when stored open to air and light.

Periodic analyses of the dose formulations of diethanolamine were conducted at the study laboratory using GC/FID. Dose formulations were analyzed approximately every 9 weeks (Table F2). Of the dose formulations analyzed and used for rats, 98% (48/49) were within 10% of the target concentration. The single dose that was out of range (+17%) was accidentally used for dosing; however, subsequent reanalysis of this dose formulation and analysis of the animal room sample from the same dose formulation showed that this dose was actually within 10% of the target concentration. All dose formulations for mice and all animal room samples for rats and mice were within 10% of the target concentrations.

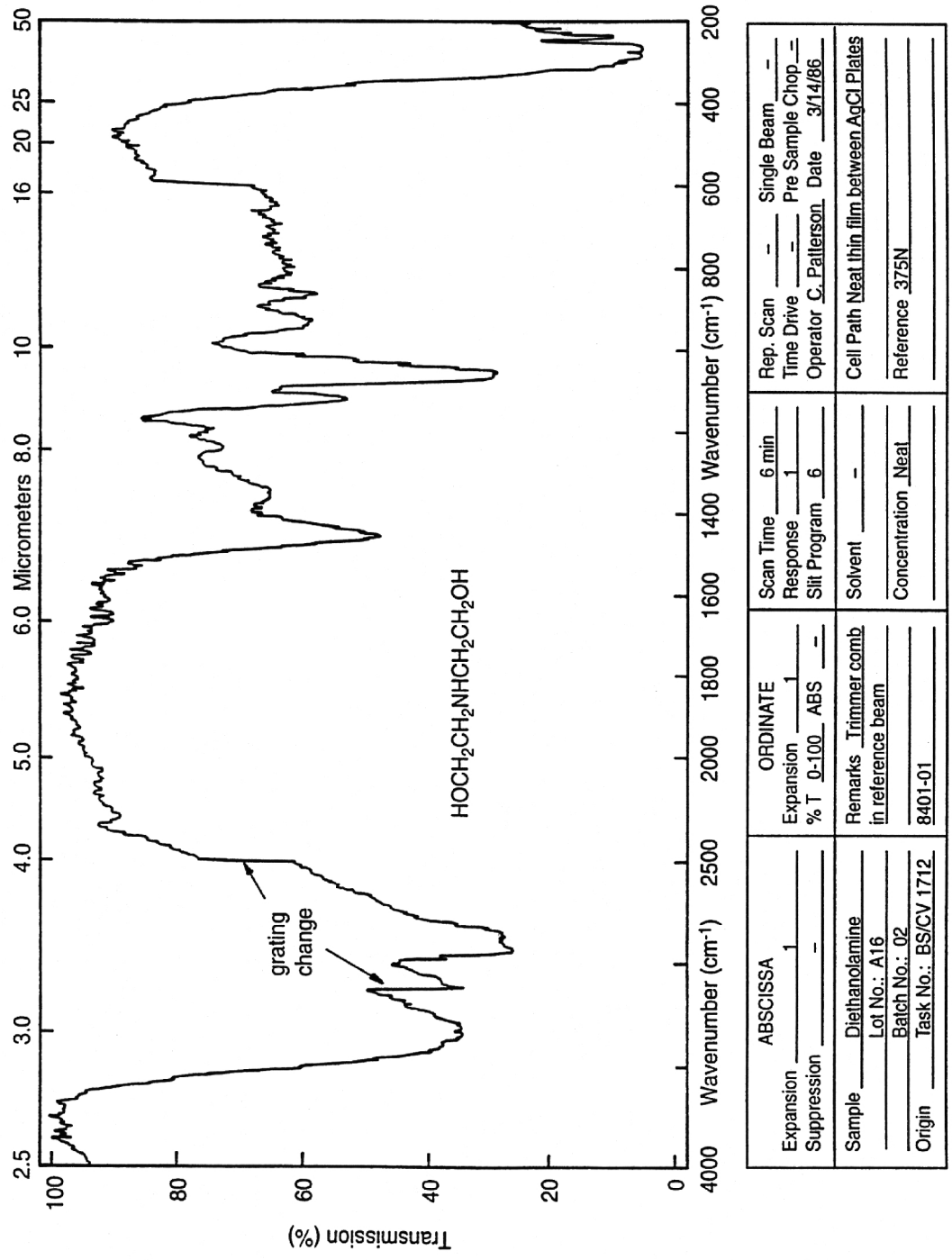

FIGURE F1
Infrared Absorption Spectrum of Diethanolamine

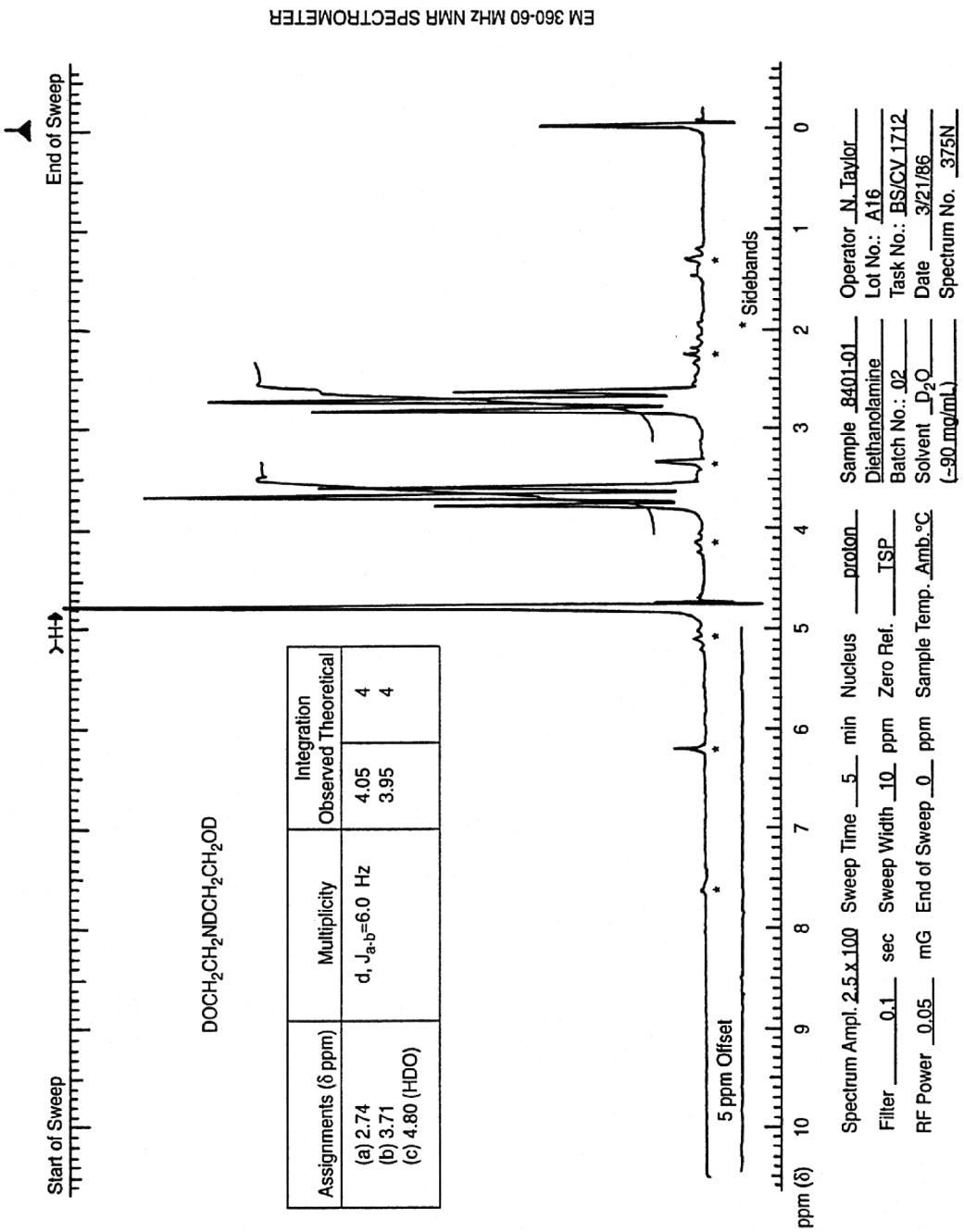

FIGURE F2
Nuclear Magnetic Resonance Spectrum of Diethanolamine

TABLE F1
Preparation and Storage of Dose Formulations in the 2-Year Dermal Studies of Diethanolamine

Preparation
Doses were prepared by weighing the appropriate amount of diethanolamine and mixing it by shaking with 95% ethanol. Doses were prepared every 3 weeks.

Chemical Lot Number
A16

Maximum Storage Time
28 days

Storage Conditions
Stored in amber glass bottles at room temperature, protected from light

Study Laboratory
Battelle Columbus Laboratories
(Columbus, OH)

Referee Laboratory
None

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diethanolamine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats			
4 October 1990	13.8	14.7	+7
	27.5	28.5	+4
	55.0	56.3	+2
	110	112	+2
4 October 1990[b]	13.8	14.6	+6
	27.5	29.7	+8
	55.0	58.9	+7
	110	118	+7
17 December 1990	13.8	16.2[c]	+17
	27.5	28.9	+5
	55.0	56.6	+3
	110	115	+5
18 February 1991	13.8	13.5	−2
	27.5	27.3	−1
	55.0	54.7	−1
	110	111	+1
22 April 1991	13.8	15.1	+9
	27.5	28.2	+3
	27.5	27.8	+1
	55.0	57.3	+4
	110	115	+5
22 April 1991[b]	13.8	14.1	+2
	27.5	28.7	+4
	55.0	58.5	+6
	110	116	+5
24 June 1991	13.8	14.3[d]	+4
	27.5	27.9	+1
	55.0	55.6	+1
	110	112	+2
26 August 1991	13.8	13.3	−4
	27.5	28.0	+2
	55.0	55.4	+1
	110	112	+2

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diethanolamine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)			
28 October 1991	13.8	13.4	−3
	27.5	27.0	−2
	55.0	54.0	−2
	110	112	+2
28 October 1991[b]	13.8	13.9	+1
	27.5	27.3	−1
	55.0	56.6	+3
	110	116	+5
30 December 1991	13.8	14.3	+4
	27.5	28.5	+4
	55.0	56.1	+2
	110	114	+4
2 March 1992	13.8	13.1	−5
	27.5	26.5	−4
	55.0	55.1	0
	110	111	+1
4 May 1992	13.8	13.7	−1
	27.5	28.3	+3
	55.0	56.4	+3
	110	111	+1
4 May 1992[b]	13.8	14.2	+3
	27.5	29.4	+7
	55.0	55.3	+1
	110	114	+4
6 July 1992	13.8	14.0	+1
	27.5	28.7	+4
	55.0	55.7	+1
	110	109	−1
8 September 1992	13.8	14.0	+1
	27.5	28.1	+2
	55.0	57.4	+4
	110	106	−4

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diethanolamine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice			
17 October 1990	22.5	22.3	−1
	45.0	45.4	+1
	90.0	93.6	+4
17 October 1990[b]	22.5	22.6	0
	45.0	45.2	0
	90.0	90.5	+1
17 December 1990	22.5	23.4	+4
	45.0	46.0	+2
	90.0	92.3	+3
18 February 1991	22.5	22.7	+1
	45.0	44.6	−1
	90.0	91.5	+2
22 April 1991	22.5	23.4	+4
	45.0	44.8	0
	90.0	93.8	+4
22 April 1991[b]	22.5	22.7	+1
	45.0	45.4	+1
	90.0	92.5	+3
24 June 1991	22.5	23.2	+3
	45.0	45.8	+2
	90.0	90.4	0
26 August 1991	22.5	22.7	+1
	45.0	45.8	+2
	90.0	91.2	+1
28 October 1991	22.5	21.1	−6
	45.0	45.0	0
	90.0	91.0	+1
28 October 1991[b]	22.5	22.9	+2
	45.0	46.5	+3
	90.0	92.9	+3
30 December 1991	22.5	23.5	+4
	45.0	45.8	+2
	90.0	92.9	+3
2 March 1992	22.5	22.0	−2
	45.0	44.1	−2
	90.0	90.4	0

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diethanolamine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)			
4 May 1992	22.5	22.6	0
	45.0	45.6	+1
	90.0	93.8	+4
4 May 1992[b]	22.5	23.4	+4
	45.0	45.8	+2
	90.0	95.6	+6
6 July 1992	22.5	22.9	+2
	45.0	45.5	+1
	90.0	93.0	+3
8 September 1992	22.5	22.8	+1
	45.0	45.8	+2
	90.0	91.5	+2

[a] Results of duplicate analysis. For rats, dosing volumes ranged from 76 to 267 μL (males) and 61 to 173 μL (females); 13.8 mg/mL=8 mg/kg, 27.5 mg/mL=16 mg/kg, 55.0 mg/mL=32 mg/kg, and 110 mg/mL=64 mg/kg. For mice, dosing volumes ranged from 41 to 93 μL (males) and 34 to 91 μL (females); 22.5 mg/mL=40 mg/kg, 45 mg/mL=80 mg/kg, and 90 mg/mL=160 mg/kg.
[b] Animal room samples
[c] Formulation was accidentally released for dosing. Subsequent reanalysis of the dose formulation and animal room sample indicated a concentration of 15.1 mg/mL, which was within 10% of the target concentration.
[d] Mean of four analyses

APPENDIX G
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE G1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE G2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE G3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.43 ± 0.52	22.3 — 24.3	24
Crude fat (% by weight)	5.32 ± 0.19	5.00 — 5.90	24
Crude fiber (% by weight)	3.36 ± 0.33	2.60 — 4.30	24
Ash (% by weight)	6.45 ± 0.19	6.12 — 6.81	24
Amino Acids (% total diet)			
Arginine	1.273 ± 0.083	1.100 — 1.390	12
Cystine	0.307 ± 0.068	0.181 — 0.400	12
Glycine	1.152 ± 0.051	1.060 — 1.220	12
Histidine	0.581 ± 0.029	0.531 — 0.630	12
Isoleucine	0.913 ± 0.034	0.867 — 0.965	12
Leucine	1.969 ± 0.053	1.850 — 2.040	12
Lysine	1.269 ± 0.050	1.200 — 1.370	12
Methionine	0.436 ± 0.104	0.306 — 0.699	12
Phenylalanine	0.999 ± 0.114	0.665 — 1.110	12
Threonine	0.899 ± 0.059	0.824 — 0.985	12
Tryptophan	0.216 ± 0.146	0.107 — 0.671	12
Tyrosine	0.690 ± 0.091	0.564 — 0.794	12
Valine	1.079 ± 0.057	0.962 — 1.170	12
Essential Fatty Acids			
Linoleic	2.389 ± 0.223	1.830 — 2.570	11
Linolenic	0.273 ± 0.034	0.210 — 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,692 ± 1,376	5,280 — 11,450	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5 — 48.9	12
Thiamine (ppm)	17.67 ± 2.06	14.0 — 22.0	24
Riboflavin (ppm)	7.78 ± 0.899	6.10 — 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0 — 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0 — 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60 — 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80 — 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190 — 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6 — 65.0	12
Choline (ppm)	2,955 ± 382	2,300 — 3,430	11
Minerals			
Calcium (%)	1.16 ± 0.10	1.00 — 1.49	24
Phosphorus (%)	0.92 ± 0.05	0.760 — 1.00	24
Potassium (%)	0.886 ± 0.059	0.772 — 0.971	10
Chloride(%)	0.531 ± 0.082	0.380 — 0.635	10
Sodium (%)	0.316 ± 0.031	0.258 — 0.370	12
Magnesium (%)	0.165 ± 0.010	0.148 — 0.180	12
Sulfur (%)	0.266 ± 0.060	0.208 — 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0 — 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7 — 102.0	12
Zinc (ppm)	59.42 ± 9.73	46.1 — 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09 — 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52 — 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60 — 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49 — 1.23	8

TABLE G4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.44 ± 0.19	0.10 — 0.70	24
Cadmium (ppm)	0.14 ± 0.07	0.04 — 0.20	24
Lead (ppm)	0.35 ± 0.25	0.10 — 1.00	24
Mercury (ppm)[c]	0.02	0.02 — 0.03	24
Selenium (ppm)	0.32 ± 0.11	0.05 — 0.40	24
Aflatoxins (ppm)	<5.0		24
Nitrate nitrogen (ppm)[d]	8.91 ± 4.36	2.90 — 17.0	24
Nitrite nitrogen (ppm)[d]	0.15 ± 0.08	0.10 — 0.40	24
BHA (ppm)[e]	1.46 ± 0.93	1.00 — 5.00	24
BHT (ppm)[e]	1.29 ± 0.86	1.0 — 5.00	24
Aerobic plate count (CFU/g)	99,321 ± 165,153	4,100 — 710,000	24
Coliform (MPN/g)	3 ± 0.3	3 — 4	24
Escherichia coli (MPN/g)	<3		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[f]	7.33 ± 1.73	4.7 — 11.4	24
N-Nitrosodimethylamine (ppb)[f]	5.45 ± 1.16	2.9 — 8.2	24
N-Nitrosopyrrolidine (ppb)[f]	1.88 ± 0.98	1.0 — 4.3	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
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.25 ± 0.24	0.05 — 0.970	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[a] 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] All but three values were less than the detection limit; the detection limit was used for the low end of the range.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX H
SENTINEL ANIMAL PROGRAM

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 rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all 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 rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, 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 the blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
PVM	12 months
RCV/SDA	6 months
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination

MICE

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	12 and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
EDIM	6 and 18 months
MHV	18 months
Reovirus 3	6 and 12 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

RESULTS

Three rats had positive titers for *M. arthritidis* at the end of the study. Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in rats with positive titers. Accordingly, sporadic *M. arthritidis*-positive titers were considered to be false positives.