NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

OLEIC ACID DIETHANOLAMINE CONDENSATE

(CAS NO. 93-83-4)

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 481

NIH Publication No. 99-3971

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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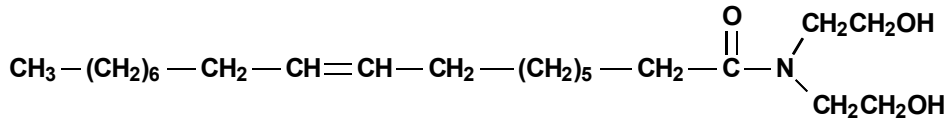
ABSTRACT



OLEIC ACID DIETHANOLAMINE CONDENSATE

CAS No. 93-83-4

Chemical Formula: $C_{22}H_{43}NO_3$ Molecular Weight: 387.68

Synonyms: Diethanolamine oleate; diethanolammonium oleate; (Z)-9-octadecenoic acid, compound with 2,2′-imnobis(ethanol) (1:1); oleamide diethanolamine

Oleic acid diethanolamine condensate is widely used as an emollient, thickener, and foam stabilizer present in cosmetic formulations of bath additives, shampoos, conditioners, lipsticks, and hair dyes. Male and female F344/N rats and B6C3F$_1$ mice received dermal applications of diethanolamine in 95% ethanol for 13 weeks or 2 years. Genetic toxicology studies were performed in *Salmonella typhimurium* and L5178Y mouse lymphoma cells.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were administered 0, 25, 50, 100, 200, or 400 mg oleic acid diethanolamine condensate/kg body weight in ethanol dermally for 13 weeks. All male and female rats survived until the end of the study. The final mean body weights and body weight gains of 200 and 400 mg/kg males and the mean body weight gain of 400 mg/kg females were significantly less than those of the vehicle controls. The only chemical-related clinical finding was irritation of the skin at the site of application in most males administered 100 mg/kg or greater and in all females administered 50 mg/kg or greater. Segmented neutrophil counts were increased relative to the vehicle controls in the 400 mg/kg male group on days 5 and 19, in the 200 mg/kg female group on day 19 and at week 13, and in the 400 mg/kg female group on days 5 and 19 and at week 13. Alkaline phosphatase concentrations were significantly increased in the 200 mg/kg male group on day 19, the 200 mg/kg female group at week 13, and in the 400 mg/kg groups of males and females at week 13. Kidney weights of 200 and 400 mg/kg females were significantly greater than those of the vehicle controls. Lesions of the skin at the site of application included epidermal hyperplasia, parakeratosis, chronic active dermal inflammation, suppurative epidermal inflammation, and sebaceous gland hypertrophy in dosed rats. The severities of these lesions generally increased with increasing dose.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were administered 0, 50, 100, 200, 400, or 800 mg oleic acid diethanolamine condensate/kg body weight in ethanol dermally for 13 weeks. All male and female mice except one 800 mg/kg male survived until the end of the study. Final mean body weights and body weight gains of 800 mg/kg males and females and 400 mg/kg females were significantly less than those of the vehicle controls. Clinical findings in dosed mice included irritation of the skin at the site of application. Irritation occurred in all surviving dosed males and in most females administered 100 mg/kg or greater and progressed to ulcer in one 800 mg/kg male. The heart weights of 400 and 800 mg/kg males and females and

200 mg/kg females and the kidney weights of 50, 100, and 400 mg/kg males were significantly greater than those of the vehicle controls. Relative to the vehicle controls, the liver weights were increased in all dosed groups. Lesions of the skin at the site of application in dosed mice included epidermal hyperplasia, parakeratosis, suppurative epidermal inflammation, chronic active dermal inflammation, sebaceous gland hypertrophy, and ulcer. The severities of these lesions generally increased with increasing dose.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were administered 0, 50, or 100 mg oleic acid diethanolamine condensate/kg body weight in ethanol dermally for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of dosed male and female rats was similar to that of the vehicle control groups. Mean body weights of 100 mg/kg males were slightly less than those of the vehicle controls throughout most of the study. Mean body weights of 100 mg/kg females were less than those of the vehicle controls beginning at week 24. The only significant treatment-related clinical finding was mild to moderate irritation of the skin at the site of application in dosed males and females.

Pathology Findings

The predominant effects of oleic acid diethanolamine condensate administration were minimal to moderate nonneoplastic lesions of the skin at the site of application in dosed rats. These lesions included epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, parakeratosis, chronic active dermal inflammation, and ulcer.

2-YEAR STUDY IN MICE

Groups of 55 male and 55 female mice were administered 0, 15, or 30 mg oleic acid diethanolamine condensate/kg body weight in ethanol dermally for 2 years. Five animals from each group were evaluated at 3 months for gross lesions and skin histopathology.

Survival, Body Weights, and Clinical Findings

Survival of dosed male and female mice was similar to that of the vehicle control groups. Mean body weights of dosed males and of 15 mg/kg females were similar to those of the vehicle controls throughout the study. Mean body weights of 30 mg/kg females were less than those of the vehicle controls from week 76 until the end of the study. The only significant treatment-related clinical finding was irritation of the skin at the site of application in 30 mg/kg males.

Pathology Findings

The incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and chronic active inflammation of the dermis in all dosed groups were significantly increased relative to the vehicle controls at 3 months and at 2 years. The increased incidences of hyperkeratosis in dosed males at 3 months and in dosed males and females at 2 years, of parakeratosis in 30 mg/kg males at 3 months and 2 years, and of ulcer in 30 mg/kg males and exudate in 30 mg/kg males and females at 2 years were also attributed to chemical administration.

GENETIC TOXICOLOGY

Oleic acid diethanolamine condensate was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation enzymes. In addition, it did not induce mutations in mouse L5178Y lymphoma cells treated with or without S9.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of oleic acid diethanolamine condensate in male or female F344/N rats administered 50 or 100 mg/kg or in male or female B6C3F$_1$ mice administered 15 or 30 mg/kg.

Dermal administration of oleic acid diethanolamine condensate to male and female rats was associated with epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, parakeratosis, chronic active inflammation of the dermis, and ulceration of the skin

at the site of application. Dermal administration of oleic acid diethanolamine condensate to mice was associated with epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, chronic active inflammation of the dermis, and exudate of the skin at the site of application in males and females and parakeratosis and ulcer of the skin at the site of application in males.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses in ethanol by dermal application	0, 50, or 100 mg/kg	0, 50, or 100 mg/kg	0, 15, or 30 mg/kg	0, 15, or 30 mg/kg
Body weights	100 mg/kg group slightly less than vehicle control group	100 mg/kg group less than vehicle control group	Dosed groups similar to vehicle control group	30 mg/kg group less than vehicle control group
Survival rates	8/50, 10/50, 14/50	15/50, 18/50, 14/50	41/49, 35/50, 34/50	34/50, 30/50, 35/50
Nonneoplastic effects	Skin (site of application): epidermal hyperplasia (0/50, 49/50, 47/50); sebaceous gland, hyperplasia (1/50, 45/50, 45/50); hyperkeratosis (0/50, 44/50, 40/50); parakeratosis (0/50, 10/50, 11/50); chronic active dermal inflammation (0/50, 48/50, 41/50); ulcer (0/50, 7/50, 6/50)	Skin (site of application): epidermal hyperplasia (3/50, 50/50, 50/50); sebaceous gland, hyperplasia (2/50, 48/50, 49/50); hyperkeratosis (1/50, 38/50, 31/50); parakeratosis (2/50, 27/50, 43/50); chronic active dermal inflammation (2/50, 44/50, 48/50); ulcer (3/50, 20/50, 36/50)	Skin (site of application): epidermal hyperplasia (1/49, 40/50, 47/50); sebaceous gland hyperplasia (1/49, 21/50, 34/50); hyperkeratosis (1/49, 38/50, 37/50); parakeratosis (0/49, 2/50, 8/50); chronic active dermal inflammation (0/49, 34/50, 50/50); ulcer (0/49, 0/50, 7/50); exudate (1/49, 3/50, 9/50)	Skin (site of application): epidermal hyperplasia (0/50, 43/50, 50/50); sebaceous gland hyperplasia (0/50, 39/50, 46/50); hyperkeratosis (0/50, 36/50, 42/50); chronic active dermal inflammation (0/50, 40/50, 49/50); exudate (0/50, 0/50, 6/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, and TA1535			
Mouse lymphoma gene mutations:	Negative with and without S9			

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 oleic acid diethanolamine condensate 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 carcinogenesis studies of oleic acid diethanolamine condensate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of oleic acid diethanolamine condensate by discussing the uses of the chemical and the 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 or female F344/N rats or male or female B6C3F$_1$ mice.

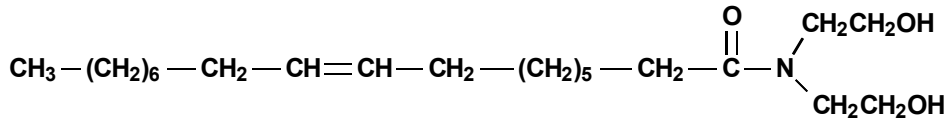
Dr. Goldsworthy, a principal reviewer, agreed in principle with the proposed conclusions. He asked whether equivocal evidence was considered for the occurrence of interstitial cell adenoma of the testis in male rats. He noted that this response appeared to be increased with respect to the most suitable controls, the concurrent controls and those from the three other diethanolamine studies. Dr. J.K. Haseman, NIEHS, responded that one of the two dermal studies in the historical database had a control rate for testicular neoplasms in rats that was higher than the rate in the 100 mg/kg group in this study. Also, no increases in the incidences of these neoplasms were seen in the three other diethanolamine studies.

Dr. I. Russo, the second principal reviewer, agreed with the proposed conclusions. She wondered if the neoplastic responses in this study would have been similar to those in the two other diethanolamine condensate studies if the free diethanolamine content had been similar rather than lower. She suggested the addition of a graph showing the diethanolamine content of each condensate (Figure 5, p. 48).

Dr. Carlson and others expressed concern about the large number of impurities in the test material. Dr. C.S. Smith, NIEHS, noted that the results of the purity analyses were in the appendix and that the impurities were mainly other fatty acids, free diethanolamines, or unidentifiable organic impurities. Dr. J.R. Bucher, NIEHS, said that the NTP would determine if there is a purity grade material designation for these diethanolamides and, if so, that information would be added to the title of each Technical Report.

Dr. Goldsworthy moved that the Technical Report on oleic acid diethanolamine condensate be accepted with the revisions discussed and the conclusions as written for male and female mice, *no evidence of carcinogenic activity*. Dr. I. Russo seconded the motion, which was accepted by seven yes votes and one abstention (Dr. Bus).

INTRODUCTION



OLEIC ACID DIETHANOLAMINE CONDENSATE

CAS No. 93-83-4

Chemical Formula: $C_{22}H_{43}NO_3$ Molecular Weight: 387.68

Synonyms: Diethanolamine oleate; diethanolammonium oleate; (Z)-9-octadecenoic acid, compound with 2,2′-imnobis(ethanol) (1:1); oleamide diethanolamine

CHEMICAL AND PHYSICAL PROPERTIES

Oleic acid diethanolamine condensate is an amber-colored liquid at room temperature and standard pressure. It is soluble in alcohols, glycols, ketones, chlorinated solvents, and other aliphatic hydrocarbon solvents. It may contain from 6% to 7.5% free oleic acid. Oleic acid diethanolamine condensate has a specific gravity of 0.99 and undergoes a phase transition from liquid to solid at −8° C, but other physical properties have not been well characterized (CTFA, 1985).

PRODUCTION, USE, AND HUMAN EXPOSURE

Oleic acid diethanolamine condensate is produced by the condensation of oleic acid and diethanolamine. Like other fatty acid diethanolamides, oleic acid diethanolamine condensate is widely used in cosmetics as an emollient, thickener, and foam stabilizer and is present in approximately 121 cosmetic formulations of bath additives, shampoos, conditioners, lipsticks, and hair dyes. In these formulations, the concentration of diethanolamide ranges from 0.1% to 25%. Oleic acid diethanolamine condensate is also used as the active ingredient in preparations designed for the treatment of seborrhea and acne; in these preparations it is present at concentrations ranging from 1% to 10%. Other applications include use as a surfactant in bar soaps, light-duty detergents, and dishwashing detergents (CTFA, 1985).

The National Occupational Exposure Survey estimated that 103,140 workers are potentially exposed to oleic acid diethanolamine condensate annually (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

No information is available on the absorption, distribution, metabolism, or excretion of oleic acid diethanolamine condensate in experimental animals or in humans. Free oleic acid present as a contaminant in oleic acid diethanolamine condensate would be metabolized by β-oxidation (Lehninger, 1982).

TOXICITY

Experimental Animals

Only acute toxicity data are available for oleic acid diethanolamine condensate; for male and female Sprague-Dawley rats, the oral LD_{50} was determined to be 12.4 mL/kg body weight. The LD_{50} for a single oral dose of a diethanolamide of steric and oleic acids

was determined to be greater than 5 g/kg for rats and greater than 10 g/kg for mice (CTFA, 1985).

Humans

No references to toxicity in humans were found in a review of the current literature on oleic acid diethanolamine condensate.

CARCINOGENICITY

No references to carcinogenicity in experimental animals or in humans were found in a review of the current literature on oleic acid diethanolamine condensate.

GENETIC TOXICITY

Oleic acid diethanolamine condensate was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without exogenous metabolic activation (S9) (Zeiger *et al.*, 1988; Table E1). Furthermore, oleic acid was tested in this same assay and no evidence for mutagenic activity was observed (Mortelmans *et al.*, 1986). Oleic acid, fed in measured amounts to human volunteers for 3 weeks as part of a dietary study of the effects of various fatty acids, did not alter the frequency of micronucleated lymphocytes in peripheral blood (Record *et al.*, 1992). In addition, oleic acid did not induce oxidative damage in isolated DNA (de Kok *et al.*, 1994).

STUDY RATIONALE

Oleic acid diethanolamine condensate is widely used in cosmetics, shampoos, soaps, and related consumer products to which there is extensive human exposure. These products are typically used on a daily basis for the majority of the human lifespan. Because of the lack of information about potential risks associated with long-term exposure, oleic acid diethanolamine condensate, coconut oil acid diethanolamine condensate, and lauric acid diethanolamine condensate were selected as representatives of the diethanolamide class for evaluation of toxicity and carcinogenic potential. Because diethanolamine is a frequent contaminant of commercial preparations of diethanolamides, the toxicity and carcinogenic potential of diethanolamine were also evaluated.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Oleic Acid Diethanolamine Condensate

Oleic acid diethanolamine condensate was obtained from Henkel Corporation, Emery Group (Cincinnati, OH) in one lot (1H01722285), which was used during the 13-week and 2-year studies. Identity and purity analyses were conducted by the study laboratory (Appendix I). Stability studies were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the oleic acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear liquid, was identified as oleic acid diethanolamine condensate by infrared spectroscopy. The purity of lot 1H01722285 was determined by high-performance liquid chromatography, which revealed a major peak and 16 smaller peaks with areas of 0.5% or less relative to the major peak area. The oleic acid diethanolamine condensate content was 47.5%.

The impurities in lot 1H01722285 were further analyzed by high-performance liquid chromatography/mass spectrometry. Impurities were identified as other fatty acid alkanolamides (approximately 30%), and remaining peaks were either other fatty acids or unidentified organic impurities. Polar and nonpolar nitrosamines were analyzed with high-performance liquid chromatography with a thermo-energy analyzer. Nitrosodiethanolamine was identified at a concentration of 68 ppb. No nonpolar nitrosamines were found. Free diethanolamine was estimated at 0.19% based on the amine value supplied by the manufacturer.

Stability studies were performed by the analytical chemistry laboratory on lot DA-021 (not used) with gas chromatography. Results indicated that oleic acid diethanolamine condensate was stable when stored up to 2 weeks at 25° C. Samples stored at 60° C were not stable. The bulk chemical was stored in amber glass bottles with Teflon®-lined lids, protected from light, at room temperature throughout the studies. Stability was monitored at the end of the 13-week studies and throughout the 2-year studies with high-performance liquid chromatography. No degradation of bulk chemical was detected.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY) in eleven lots. The stability was monitored by the study laboratory throughout the studies by gas chromatography. United States Pharmacopeia ethanol reference standards were analyzed concomitantly. In comparison to the reference standard, purity of the bulk ethanol ranged from 97% to 103% except for one sample taken during the 2-year studies, which measured 110%. The result for this sample was considered to be spurious because analysis of the same material approximately 2 months later indicated a relative purity of 101%. No volatile impurities were detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by mixing oleic acid diethanolamine condensate with 95% ethanol to give the desired concentration (Table I1). The dose formulations were stored at room temperature, protected from light, in amber glass bottles for up to 28 days.

Stability studies of a 10 mg/mL formulation prepared from lot CH1F980 (not used) were performed by the study laboratory using high-performance liquid chromatography. Stability of the dose formulation was confirmed for at least 28 days when stored in sealed containers, protected from ultraviolet light, at up to room temperature or for 3 hours when stored open to air and light.

Periodic analyses of the dose formulations of oleic acid diethanolamine condensate were conducted at the study laboratory using high-performance liquid

chromatography. During the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies. All of the dose formulations and animal room samples analyzed for rats and mice were within 10% of the target concentration. During the 2-year studies, dose formulations were analyzed approximately every 9 weeks. For rats, 92% (22/24) of the dose formulations were within 10% of the target concentration; the two formulations that were not within 10% were remixed, analyzed, and found to be within specification. All dose formulations for mice and all animal room samples for rats and mice were within 10% of the target concentrations.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to oleic acid diethanolamine condensate and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 21 to 24 days and were approximately 8 weeks old on the first day of the studies. Near the end of the prestudy quarantine period, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats were administered dermal doses of 0, 25, 50, 100, 200, or 400 mg oleic acid diethanolamine condensate/kg body weight in ethanol by the application of solutions containing 0, 30, 61, 121, 243, or 485 mg/mL. Additional groups of 10 male and 10 female rats designated for day 5 or day 19 hematology and clinical chemistry analyses were also administered dermal doses of 0, 25, 50, 100, 200, or 400 mg/kg. Groups of 10 male and 10 female mice were administered dermal doses of 0, 50, 100, 200, 400, or 800 mg/kg in ethanol by the application of solutions containing 0, 20, 40, 80, 160, or 320 mg/mL. Dose volumes were adjusted based on group mean body weights to provide an appropriate mg/kg dose. Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly for rats and mice. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected from special study rats on days 5 or 19 of the study and from core study rats at study termination. Blood was collected via the retroorbital sinus under carbon dioxide/oxygen anesthesia. Blood samples for hematology parameters were collected in micro collection tubes containing potassium EDTA as an anticoagulant (Sarstedt, Inc., Germany). Blood samples for clinical chemistry evaluations were collected in micro collection serum separator tubes (Sarstedt, Inc.); serum was obtained by centrifugation. All hematology parameters except differential leukocyte and reticulocyte counts were measured with a Serono-Baker System 9000 hematology analyzer (Serono-Baker Diagnostics, Allentown, PA). Differential leukocyte counts were determined microscopically from blood smears stained with modified Wright-Giemsa. Reticulocyte counts were determined from blood smears prepared from new methylene blue-stained whole blood. Clinical chemistry parameters were measured on a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using commercially available reagents.

At the end of the 13-week studies, samples were collected for sperm motility and vaginal cytology evaluations on rats administered 0, 100, 200, or 400 mg/kg and on mice administered 0, 200, 400, or 800 mg/kg. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the

epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study rats and on all mice. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination 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. A complete histopathologic examination was performed on vehicle control and 400 mg/kg rats and on vehicle control and 800 mg/kg mice. Gross lesions and skin were examined in all other dose groups. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats were administered dermal doses of 0, 50, or 100 mg/kg in ethanol by the application of solutions containing 0, 85, or 170 mg/mL. Groups of 55 male and 55 female mice were administered dermal doses of 0, 15, or 30 mg/kg in ethanol by the application of solutions containing 0, 7.5, or 15 mg/mL. Dose volumes were adjusted based on group mean body weights to provide an appropriate mg/kg dose. Five male and five female mice from each group were evaluated at 3 months for gross lesions and skin histopathology.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 to 14 days 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 were approximately 7 weeks old and mice were approximately 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 K).

Animal Maintenance

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

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly and at the end of the studies. Body weights were recorded initially, weekly for the first 13 weeks, approximately monthly thereafter, and again at the end of the studies.

At the 3-month interim evaluation, mice were necropsied and skin from the site of application was examined microscopically.

A complete necropsy and microscopic examination were performed on all 2-year study 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. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were

entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the skin (overall) and skin from the site of application from male and female rats and mice, the forestomach and testis of male rats, and the liver of male and female mice.

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

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Oleic Acid Diethanolamine Condensate

13-Week Studies	2-Year Studies
Study Laboratory Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source Taconic Farms (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies Rats: 23 days (males) or 24 days (females) Mice: 21 days (males) or 22 days (females)	Rats: 13 days (males) or 14 days (females) Mice: 11 days (males) or 12 days (females)
Average Age When Studies Began 8 weeks	Rats: 7 weeks Mice: 6 weeks
Date of First Dose Rats: 25 June 1992 (males) 26 June 1992 (females) Mice: 23 June 1992 (males) 24 June 1992 (females)	Rats: 19 May 1993 (males) 20 May 1993 (females) Mice: 10 May 1993 (males) 11 May 1993 (females)
Duration of Dosing Five exposures per week for 13 weeks	Five exposures per week for 104 (rats) or 105 (mice) weeks
Date of Last Dose Rats: 23 September 1992 (males) 24 September 1992 (females) Mice: 21 September 1992 (males) 22 September 1992 (females)	Rats: 15 May 1995 (males) 16 May 1995 (females) Mice: 3-Month interim evaluation 10 August 1993 (males) 11 August 1993 (females) Terminal sacrifice 8 May 1995 (males) 10 May 1995 (females)
Necropsy Dates Rats: 24 September 1992 (males) 25 September 1992 (females) Mice: 22 September 1992 (males) 23 September 1992 (females)	Rats: 16 May 1995 (males) 17 May 1995 (females) Mice: 3-Month interim evaluation 11 August 1993 (males) 12 August 1993 (females) Terminal sacrifice 8-9 May 1995 (males) 10-11 May 1995 (females)
Average Age at Necropsy 21 weeks	20 weeks (3-month interim evaluation mice) 111 weeks (rats and terminal mice)
Size of Study Groups 10 males and 10 females	50 males and 50 females 5 males and 5 females (3-month interim evaluation mice)

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Oleic Acid Diethanolamine Condensate

13-Week Studies	2-Year Studies
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 13-week studies
Animals per Cage 1	1
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 13-week studies
Water Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 13-week studies
Cages Polycarbonate (Lab Products, Inc., Maywood, NJ), changed weekly	Same as 13-week studies
Bedding Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed weekly	Same as 13-week studies
Cage Filters DuPont 2024 spun-bonded polyester fiber (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 13-week studies
Racks Stainless steel (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks	Same as 13-week studies
Animal Room Environment Temperature: 21.1°-22.8° C (rats) 20.6°-25.6° C (mice) Relative humidity: 37%-65% (rats) 39%-65% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 21.1°-23.3° C (rats) 21.1°-25.0° C (mice) Relative humidity: 31%-73% (rats) 36%-68% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour
Doses Rats: 0, 25, 50, 100, 200, or 400 mg/kg (0, 30, 61, 121, 243, or 485 mg/mL in ethanol) applied to the shaved intrascapular skin Mice: 0, 50, 100, 200, 400, or 800 mg/kg (0, 20, 40, 80, 160, or 320 mg/mL in ethanol) applied to the shaved intrascapular skin	Rats: 0, 50, or 100 mg/kg (0, 85, or 170 mg/mL in ethanol) Mice: 0, 15, or 30 mg/kg (0, 7.5, or 15 mg/mL in ethanol)
Type and Frequency of Observation Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly.	Observed twice daily; animals were weighed initially, weekly for 13 weeks, approximately monthly thereafter, and again at the end of the studies; clinical findings were recorded monthly and at the end of the studies.
Method of Sacrifice CO_2 asphyxiation	Same as 13-week studies

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Oleic Acid Diethanolamine Condensate

13-Week Studies	2-Year Studies
Necropsy Necropsy was performed on all core study rats and all mice. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals.
Clinical Pathology Blood was collected via the retroorbital sinus of special study rats on days 5 or 19 and all core study rats surviving to the end of the studies ***Hematology:*** hematocrit; hemoglobin; erythrocyte, nucleated erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte counts and differentials ***Clinical chemistry:*** Urea nitrogen, creatinine, alanine aminotransferase, alkaline phosphatase, sorbitol dehydrogenase, total protein, albumin, and bile salts	None
Histopathology Complete histopathology was performed on 0 and 400 mg/kg rats and on 0 and 800 mg/kg mice. In addition to gross lesions and tissue masses, the following tissues were examined: 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, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, skin from the site of application was examined in all dose groups.	Skin from the site of application was examined from all mice at the 3-month interim evaluation. Complete histopathology was performed on all rats and mice at the end of the studies. In addition to gross lesions and tissue masses, the following tissues were examined: 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, 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.
Sperm Motility and Vaginal Cytology At the end of the studies, sperm samples were collected from all male rats administered 0, 100, 200, or 400 mg/kg and male mice administered 0, 200, 400, or 800 mg/kg for sperm motility evaluations. The following parameters were evaluated: sperm concentration, sperm motility, sperm count, spermatid heads per testis, and spermatid heads per gram of testis. The left cauda epididymis, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all female rats administered 0, 100, 200, or 400 mg/kg and female mice administered 0, 200, 400, or 800 mg/kg for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stage.	None

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, B4, C1, C4, D1, and D4 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). For neoplasms and nonneoplastic lesions detected at the interim evaluation, the Fisher exact test (Gart *et al.,* 1979), a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed

distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

QUALITY ASSURANCE METHODS

The 13-week and 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 oleic acid diethanolamine condensate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and in L5178Y mouse lymphoma cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of oleic acid diethanolamine condensate 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.

RESULTS

RATS

13-WEEK STUDY

All male and female rats survived until the end of the study. The final mean body weights and body weight gains of 200 and 400 mg/kg males and the mean body weight gain of 400 mg/kg females were significantly less than those of the vehicle controls (Table 2). The only chemical-related clinical finding was irritation of the skin at the site of application in most males administered 100 mg/kg or greater and in all females administered 50 mg/kg or greater.

Segmented neutrophil counts were increased relative to the vehicle controls in the 400 mg/kg male group on days 5 and 19, in the 200 mg/kg female group on day 19 and at week 13, and in the 400 mg/kg female group on days 5 and 19 and at week 13 (Table F1). Alkaline phosphatase concentrations were significantly increased in the 200 mg/kg male group on day 19, in the 200 mg/kg female group at week 13, and in the 400 mg/kg groups of males and females at week 13 (Table F1). There were no biologically significant differences in sperm motility or vaginal cytology parameters between dosed and vehicle control rats (Tables H1 and H2).

TABLE 2
Survival and Body Weights of Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	189 ± 3	355 ± 5	166 ± 5	
25	10/10	190 ± 4	357 ± 5	167 ± 5	101
50	10/10	189 ± 3	357 ± 7	168 ± 6	101
100	10/10	192 ± 4	349 ± 7	158 ± 4	98
200	10/10	191 ± 4	330 ± 5**	140 ± 4**	93
400	10/10	190 ± 4	295 ± 8**	106 ± 8**	83
Female					
0	10/10	135 ± 3	195 ± 5	60 ± 3	
25	10/10	138 ± 3	194 ± 6	56 ± 6	99
50	10/10	136 ± 2	198 ± 4	62 ± 2	102
100	10/10	137 ± 2	193 ± 3	56 ± 3	99
200	10/10	137 ± 3	190 ± 4	52 ± 2	97
400	10/10	136 ± 2	187 ± 4	51 ± 2*	96

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Kidney weights of 200 and 400 mg/kg females were increased relative to the vehicle controls (Table G1). Reduced heart, liver, and thymus weights of 400 mg/kg males and lung and thymus weights of 200 and 400 mg/kg females were associated with the lower mean body weights of these groups.

Nonneoplastic lesions of the skin related to administration of oleic acid diethanolamine condensate included epidermal hyperplasia, parakeratosis, chronic active inflammation of the dermis, suppurative epidermal inflammation, and sebaceous gland hypertrophy in males and females (Table 3). The severities of epidermal hyperplasia and sebaceous gland hypertrophy increased with increasing dose in males and females.

Dose Selection Rationale: Generally, doses of 200 and 400 mg/kg were associated with reduced mean body weights and body weight gains as well as high incidences of lesions of the skin at the site of application in both male and female rats. Based on this response, these doses were considered inappropriate for a 2-year study. Lesions of the skin were also present at the site of application in groups administered 100 mg/kg; however, the incidences were somewhat less than those observed in the 200 and 400 mg/kg groups. In addition, the severities of the lesions were increased only slightly in the 200 and 400 mg/kg groups compared to the severities in the 100 mg/kg groups. Moreover, it was considered unlikely that these lesions would progress and become life threatening over the period of a 2-year study. Therefore, 100 mg/kg was selected as the high dose for rats in the 2-year study. In groups treated with 50 mg/kg, the incidences of skin lesions diminished considerably and lesion severities were minimal. Therefore, 50 mg/kg was selected as the low dose in the 2-year study.

TABLE 3
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male						
Number Examined Microscopically	10	10	10	10	10	10
Epidermal Hyperplasia[a]	0	0	7** (1.0)[b]	8** (1.8)	9** (2.0)	10** (2.2)
Parakeratosis	0	0	0	2 (1.5)	9** (1.7)	10** (1.8)
Dermal Inflammation, Chronic Active	0	0	2 (1.0)	6** (1.2)	9** (1.0)	10** (1.1)
Epidermal Inflammation, Suppurative	0	0	0	1 (2.0)	3 (1.0)	5* (1.4)
Sebaceous Gland, Hypertrophy	0	0	0	2 (1.5)	8** (1.6)	10** (2.0)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Epidermal Hyperplasia	0	0	10** (1.3)	10** (1.3)	10** (1.5)	10** (2.0)
Parakeratosis	0	0	2 (1.0)	8** (1.3)	9** (1.1)	10** (1.8)
Dermal Inflammation, Chronic Active	0	0	1 (1.0)	8** (1.0)	10** (1.0)	10** (1.0)
Epidermal Inflammation, Suppurative	0	0	0	1 (1.0)	3 (1.0)	7** (1.1)
Sebaceous Gland, Hypertrophy	0	0	0	0	6** (1.5)	10** (2.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact 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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 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.

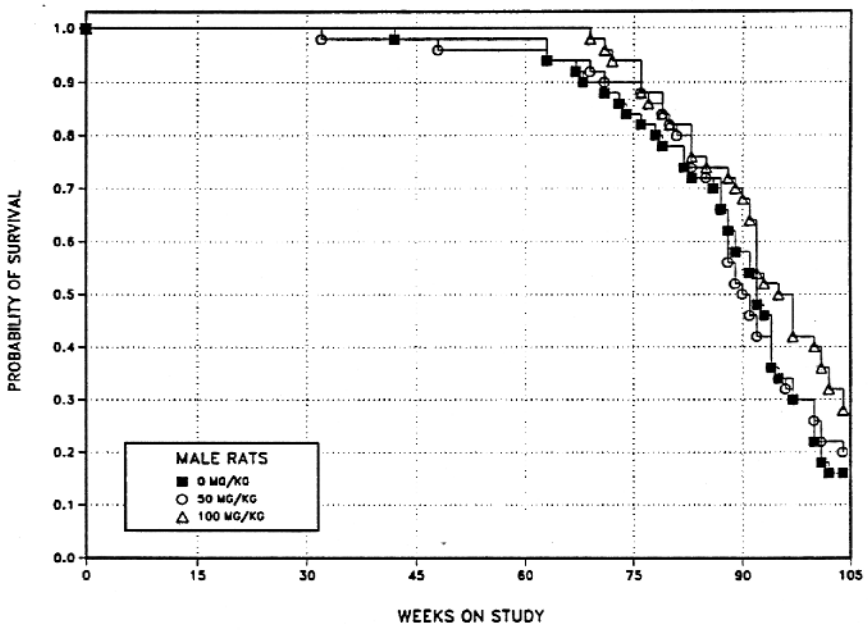
Body Weights and Clinical Findings

Mean body weights of 100 mg/kg males were slightly less than those of the vehicle control group throughout most of the study (Figure 2 and Table 5). Mean body weights of 100 mg/kg females were less than those of the vehicle controls from week 24 until the end of the study (Figure 2 and Table 6). The only significant treatment-related clinical finding was mild to moderate irritation of the skin at the site of application in dosed males and females (males: vehicle control, 0/50; 50 mg/kg, 17/50; 100 mg/kg, 32/50; females: 3/50, 46/50, 50/50).

TABLE 4
Survival of Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Animals initially in study	50	50	50
Moribund	26	30	24
Natural deaths	16	10	12
Animals surviving to study termination	8	10	14
Percent probability of survival at end of study[a]	16	20	28
Mean survival (days)[b]	622	623	651
Survival analysis[c]	P=0.125N	P=0.949N	P=0.127N
Female			
Animals initially in study	50	50	50
Moribund	11	9	5
Natural deaths	24	23	31
Animals surviving to study termination	15	18	14
Percent probability of survival at end of study	30	36	28
Mean survival (days)	627	615	567
Survival analysis	P=0.380	P=0.802N	P=0.400

[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**.



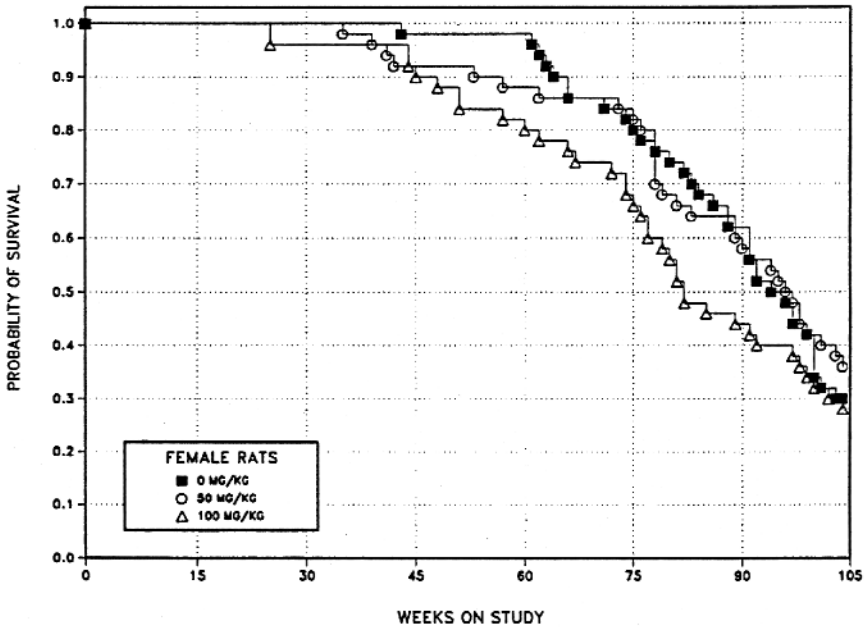


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats
Administered Oleic Acid Diethanolamine Condensate Dermally for 2 Years

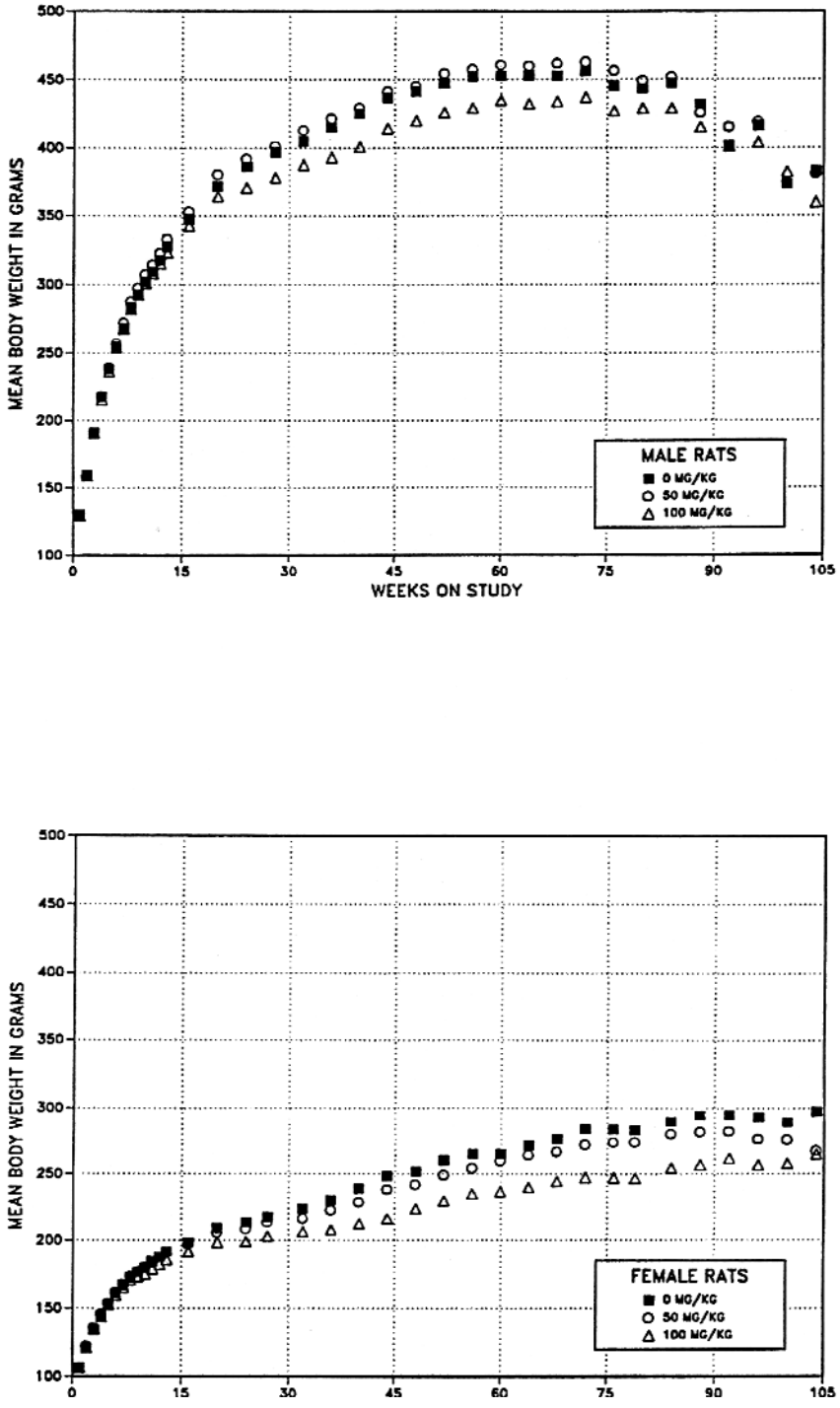


FIGURE 2
Growth Curves for Male and Female Rats
Administered Oleic Acid Diethanolamine Condensate Dermally for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

Weeks on Study	Vehicle Control		50 mg/kg			100 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
1	130	50	129	100	50	129	100	50
2	159	50	159	100	50	159	100	50
3	191	50	190	100	50	190	100	50
4	217	50	218	100	50	216	99	50
5	238	50	239	101	50	236	99	50
6	255	50	257	101	50	254	100	50
7	268	50	272	101	50	268	100	50
8	283	50	288	102	50	283	100	50
9	293	50	298	102	50	293	100	50
10	302	50	307	102	50	301	100	50
11	309	50	315	102	50	308	100	50
12	317	50	323	102	50	316	99	50
13	328	50	333	102	50	323	99	50
16	348	50	353	102	50	343	99	50
20	372	50	380	102	50	364	98	50
24	386	50	392	102	50	371	96	50
28	397	50	401	101	50	378	95	50
32	405	50	413	102	50	388	96	50
36	415	50	422	102	49	393	95	50
40	425	50	429	101	49	401	94	50
44	437	49	442	101	49	414	95	50
48	441	49	445	101	49	420	95	50
52	447	49	454	102	48	426	95	50
56	452	49	458	101	48	429	95	50
60	453	49	461	102	48	435	96	50
64	453	47	460	102	47	432	95	50
68	453	46	462	102	47	434	96	50
72	456	44	463	102	45	437	96	48
76	445	42	457	103	45	427	96	47
80	443	39	449	101	42	429	97	41
84	447	36	452	101	37	429	96	38
88	432	33	426	99	33	415	96	37
92	401	27	415	103	23	401	100	32
96	416	17	419	101	17	404	97	25
100	373	15	374	100	15	382	102	21
104	382	8	381	100	11	360	94	16
Mean for weeks								
1-13	253		256	101		252	100	
14-52	407		413	101		390	96	
53-104	431		437	101		416	97	

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

Weeks on Study	Vehicle Control		50 mg/kg			100 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
1	106	50	107	100	50	106	100	50
2	121	50	122	101	50	121	100	50
3	134	50	136	101	50	135	101	50
4	144	50	146	101	50	144	100	50
5	153	50	154	101	50	153	100	50
6	161	50	162	100	50	160	99	50
7	167	50	167	101	50	165	99	50
8	172	50	173	101	50	171	99	50
9	176	50	177	100	50	173	99	50
10	179	50	180	101	50	175	98	50
11	184	50	184	100	50	179	97	50
12	188	50	187	100	50	182	97	50
13	191	50	190	99	50	185	97	50
16	199	50	197	99	50	191	96	50
20	209	50	206	99	50	198	95	50
24	213	50	209	98	50	199	93	50
27	217	50	214	98	50	203	94	48
32	223	50	216	97	50	207	92	48
36	230	50	223	97	49	208	90	48
40	239	50	229	96	48	212	89	48
44	248	49	238	96	46	216	87	47
48	252	49	242	96	46	224	89	45
52	260	49	249	96	46	230	88	42
56	265	49	254	96	45	235	89	42
60	265	49	260	98	44	237	89	41
64	271	46	264	98	43	240	88	39
68	276	43	267	97	43	244	88	37
72	284	42	272	96	43	248	87	37
76	284	40	274	97	41	247	87	32
79	283	38	274	97	34	247	87	29
84	289	35	280	97	32	255	88	24
88	294	32	282	96	32	257	87	23
92	295	28	282	96	28	262	89	21
96	293	25	276	94	26	257	88	20
100	289	21	276	95	21	258	89	17
104	297	15	268	90	19	265	89	15
Mean for weeks								
1-13	160		160	100		158	99	
14-52	229		222	97		209	91	
53-104	283		271	96		250	88	

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, forestomach, testis, and thyroid 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: Skin neoplasms were few in number, and the incidences did not follow a pattern indicative of an association with oleic acid diethanolamine condensate administration. Neoplasms of the skin at the site of application consisted of one subcutaneous fibroma in one vehicle control male and one subcutaneous fibrosarcoma in each of the 50 and 100 mg/kg male groups (Table A1). In females, a similar incidence pattern of subcutaneous neoplasms was duplicated in the skin at other than the site of application; there were no skin neoplasms in dosed female rats at the site of application (Table B1).

The predominant effects of oleic acid diethanolamine condensate administration were minimal to moderate nonneoplastic lesions of the skin at the site of application (Tables 7, A4, and B4). The severities of these lesions were somewhat greater in dosed females than in dosed males. The major alterations from normal skin were epidermal hyperplasia (thickening of the epidermis) and sebaceous gland hyperplasia, which usually occurred along with epidermal hyperplasia; the incidences of these lesions were significantly increased in dosed males and females relative to the vehicle

TABLE 7
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Number Examined Microscopically	50	50	50
Epidermal Hyperplasia[a]	0	49** (2.0)[b]	47** (2.1)
Sebaceous Gland, Hyperplasia	1 (1.0)	45** (2.0)	45** (1.8)
Hyperkeratosis	0	44** (1.7)	40** (1.6)
Parakeratosis	0	10** (2.2)	11** (2.0)
Dermal Inflammation, Chronic Active	0	48** (1.4)	41** (1.4)
Ulcer	0	7* (2.0)	6* (2.0)
Female			
Number Examined Microscopically	50	50	50
Epidermal Hyperplasia	3 (1.3)	50** (2.3)	50** (2.4)
Sebaceous Gland, Hyperplasia	2 (2.0)	48** (2.3)	49** (2.9)
Hyperkeratosis	1 (1.0)	38** (1.5)	31** (1.5)
Parakeratosis	2 (2.0)	27** (2.1)	43** (2.3)
Dermal Inflammation, Chronic Active	2 (2.0)	44** (1.5)	48** (1.9)
Ulcer	3 (1.7)	20** (1.7)	36** (2.1)

* 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

controls (Table 7). The incidences of hyperkeratosis, parakeratosis, chronic active dermal inflammation, and ulcer in dosed males and females were also significantly increased relative to the vehicle controls. In most cases, inflammation was predominantly dermal fibrosis with few or no inflammatory cells. The skin lesions at the site of application were considered to be indicative of local irritation, with no neoplastic or preneoplastic changes.

Forestomach: The incidence of hyperkeratosis in 50 mg/kg males was significantly increased relative to the vehicle controls (Tables 8 and A4). Ulceration was also present, and in 50 mg/kg males, the incidence was greater than that in the vehicle controls, but this change was not significant and the severities of ulcer were similar among all groups. The incidence of chronic active inflammation in 50 mg/kg males was significantly greater than that in the vehicle control group; however, the incidences of these lesions were not dose related, and similar lesions were not observed in females. Therefore, these lesions were not considered to be associated with chemical exposure.

TABLE 8
Incidences of Nonneoplastic Lesions of the Forestomach in Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control		50 mg/kg		100 mg/kg	
Number Examined Microscopically	50		50		50	
Epithelial Hyperplasia[a]	14	(2.0)[b]	25	(1.8)	13	(1.9)
Hyperkeratosis	14	(2.0)	26*	(1.7)	11	(1.9)
Ulcer	10	(2.1)	14	(2.3)	7	(2.6)
Inflammation, Chronic Active	12	(2.4)	23*	(2.3)	11	(2.1)

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

Testis: The incidence of testicular interstitial cell adenoma in 100 mg/kg males was significantly greater than that in the vehicle control group (24/50, 30/50, 37/50; Table A3). Incidences of testicular interstitial cell hyperplasia were not increased (28/50, 23/50, 20/50; Table A4). Incidences of testicular adenoma vary among historical control groups. The incidences in ethanol vehicle controls from two other historical NTP dermal studies were 24 of 50 (NTP, 1998) and 42 of 52 (NTP, 1995); the latter incidence is greater than that observed at the highest dose from this study. In addition, no increases in the incidences of interstitial cell adenoma were observed in the companion studies of diethanolamine (vehicle control, 32/50; 16 mg/kg, 19/50; 32 mg/kg, 28/50; 64 mg/kg, 26/50; NTP, 1999a), coconut oil acid diethanolamine condensate (vehicle control, 23/50; 50 mg/kg, 20/50; 100 mg/kg, 19/50; NTP, 1999b), or lauric acid diethanolamine condensate (vehicle control, 20/50; 50 mg/kg, 22/50; 100 mg/kg, 17/50; NTP, 1999c). Consequently, the increased incidence of interstitial cell adenoma in this study was not considered to be chemical related.

Thyroid Gland: The incidence of follicular cell adenoma or carcinoma (combined) was increased in 50 mg/kg males relative to the vehicle control group (0/50, 6/50, 2/50; Table A3). This marginal increase was not related to dose, and no follicular cell hyperplasias were observed. Therefore, this increase was not considered to be associated with oleic acid diethanolamine condensate administration.

MICE

13-WEEK STUDY

All male and female mice except one 800 mg/kg male survived until the end of the study (Table 9). Final mean body weights and body weight gains of 800 mg/kg males and females and 400 mg/kg females were significantly less than those of the vehicle controls. Clinical findings included irritation of the skin at the site of application. Irritation occurred in all surviving dosed males and in most females administered 100 mg/kg or greater; time of onset was inversely related to dose. Irritation progressed to ulcer in one 800 mg/kg male.

Sperm motility and vaginal cytology parameters of dosed mice were similar to those of the vehicle controls (Tables H3 and H4).

The absolute and relative heart weights of 400 and 800 mg/kg males and females and 200 mg/kg females and the absolute heart weights of 50 and 100 mg/kg females were significantly greater than those of the vehicle controls (Table G2). The kidney weights of 50, 100, and 400 mg/kg males were significantly greater than those of the vehicle control group, and the liver weights were increased in all dosed groups. The absolute thymus weight of 200 mg/kg males and 400 and 800 mg/kg males and females and the relative thymus weight of 800 mg/kg females were less than those of the vehicle controls.

TABLE 9
Survival and Body Weights of Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	26.9 ± 0.4	37.8 ± 0.9	10.9 ± 0.7	
50	10/10	26.9 ± 0.4	38.9 ± 0.8	12.0 ± 0.6	103
100	10/10	26.9 ± 0.3	37.5 ± 1.0	10.6 ± 0.7	99
200	10/10	26.8 ± 0.3	36.9 ± 0.8	10.2 ± 0.8	98
400	10/10	26.4 ± 0.3	36.3 ± 0.6	10.0 ± 0.5	96
800	9/10[c]	26.7 ± 0.3	33.8 ± 0.6**	7.3 ± 0.6**	90
Female					
0	10/10	21.6 ± 0.3	32.7 ± 1.2	11.1 ± 1.0	
50	10/10	21.6 ± 0.3	33.2 ± 0.6	11.6 ± 0.5	101
100	10/10	21.7 ± 0.3	33.1 ± 0.9	11.3 ± 0.9	101
200	10/10	21.5 ± 0.3	31.6 ± 0.8	10.1 ± 0.7	97
400	10/10	21.5 ± 0.2	30.2 ± 0.6*	8.7 ± 0.5*	92
800	10/10	21.4 ± 0.3	30.6 ± 0.4*	9.2 ± 0.4*	94

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 2

Nonneoplastic lesions of the skin related to the administration of oleic acid diethanolamine condensate included epidermal hyperplasia, parakeratosis, suppurative epidermal inflammation, chronic active dermal inflammation, sebaceous gland hypertrophy, and ulcer in males and females (Table 10). The severities of these lesions generally increased with increasing dose. Bone marrow myeloid cell hyperplasia was seen in 7/10 males and 6/10 females receiving 800 mg/kg but not in any other group. The incidences of hematopoietic cell proliferation of the spleen in males receiving 800 mg/kg and in females receiving 400 and 800 mg/kg were significantly greater than those in the vehicle controls.

TABLE 10
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
Number Examined Microscopically	10	10	10	10	10	10
Epidermal Hyperplasia[a]	0	9** (1.9)[b]	10** (2.8)	10** (2.7)	10** (2.8)	10** (2.9)
Parakeratosis	0	9** (1.1)	10** (1.8)	10** (2.2)	10** (2.0)	10** (3.1)
Dermal Inflammation, Chronic Active	0	9** (1.0)	10** (1.7)	10** (2.0)	10** (2.0)	10** (2.2)
Epidermal Inflammation, Suppurative	0	9** (1.2)	9** (2.4)	10** (1.9)	10** (1.8)	10** (3.4)
Sebaceous Gland, Hypertrophy	0	9** (1.6)	10** (2.3)	10** (2.1)	10** (2.6)	10** (2.3)
Ulcer	0	2 (1.0)	6** (1.3)	9** (1.7)	8** (1.4)	10** (2.5)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Epidermal Hyperplasia	0	9** (1.1)	10** (2.2)	9** (2.9)	10** (3.0)	10** (3.4)
Parakeratosis	0	3 (1.0)	10** (1.6)	9** (2.3)	10** (2.2)	10** (3.0)
Dermal Inflammation, Chronic Active	0	8** (1.0)	10** (1.1)	9** (2.0)	10** (2.2)	10** (2.5)
Epidermal Inflammation, Suppurative	0	1 (1.0)	8** (1.1)	9** (2.4)	10** (1.9)	10** (3.0)
Sebaceous Gland, Hypertrophy	0	8** (1.1)	10** (2.0)	9** (2.1)	10** (2.5)	10** (2.6)
Ulcer	0	1 (1.0)	5* (1.0)	8** (1.5)	6** (1.5)	9** (2.1)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact 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

Dose Selection Rationale: All groups of mice administered 100 mg/kg or greater exhibited high incidences of skin lesions at the site of application; thus, doses of 100 mg/kg or greater were considered inappropriate for a 2-year study. The severities of parakeratosis and suppurative inflammation increased with increasing dose in groups administered doses greater than 100 mg/kg; however, the severities of other lesions generally were increased only slightly between 100 and 800 mg/kg compared to the eightfold increase in dose. Therefore, the skin response appeared to plateau at 100 mg/kg, and higher doses did not produce a proportional increase in response. The incidences of skin lesions in groups administered 50 mg/kg were slightly less than those observed in groups administered 100 mg/kg. The severities of lesions in the 50 mg/kg groups were mostly minimal to mild and in general were less than the severities observed in the 100 mg/kg groups. The skin response at the site of application in 50 mg/kg groups was such that 50 mg/kg was also considered inappropriate for a 2-year study; however, the slight reduction in incidences and the lower severities observed in the 50 mg/kg groups compared to those in the 100 mg/kg groups indicated that 50 mg/kg was below the plateau and at the upper end of a dose range in which skin response at the site of application exhibited a greater dose dependency. Therefore, at doses below 50 mg/kg, a proportional reduction in incidences and severities of skin lesions at the site of application would be expected. Accordingly, a high dose of 30 mg/kg and a low dose of 15 mg/kg were selected for the 2-year study in mice.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). Survival of dosed male and female mice was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of dosed males and 15 mg/kg females were similar to those of the vehicle controls throughout the study (Figure 4 and Tables 12 and 13). Mean body weights of 30 mg/kg females were less than those of the vehicle controls beginning week 76. The only significant treatment-related clinical finding was irritation of the skin at the site of application in 30 mg/kg males (vehicle control, 0/55; 15 mg/kg, 1/55; 30 mg/kg, 20/55).

TABLE 11
Survival of Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
Animals initially in study	55	55	55
3-Month interim evaluation[a]	5	5	5
Missing[a]	1	0	0
Moribund	3	8	11
Natural deaths	5	7	5
Animals surviving to study termination	41	35	34
Percent probability of survival at end of study[b]	84	70	68
Mean survival (days)[c]	693	693	680
Survival analysis[d]	P=0.086	P=0.182	P=0.102
Female			
Animals initially in study	55	55	55
3-Month interim evaluation[a]	5	5	5
Accidental death[a]	0	0	1
Moribund	8	12	8
Natural deaths	8	8	6
Animals surviving to study termination	34	30	35
Percent probability of survival at end of study	68	60	71
Mean survival (days)	684	683	687
Survival analysis	P=0.780N	P=0.561	P=0.847N

[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 negative trend or lower mortality in a dose group is indicated by **N**.

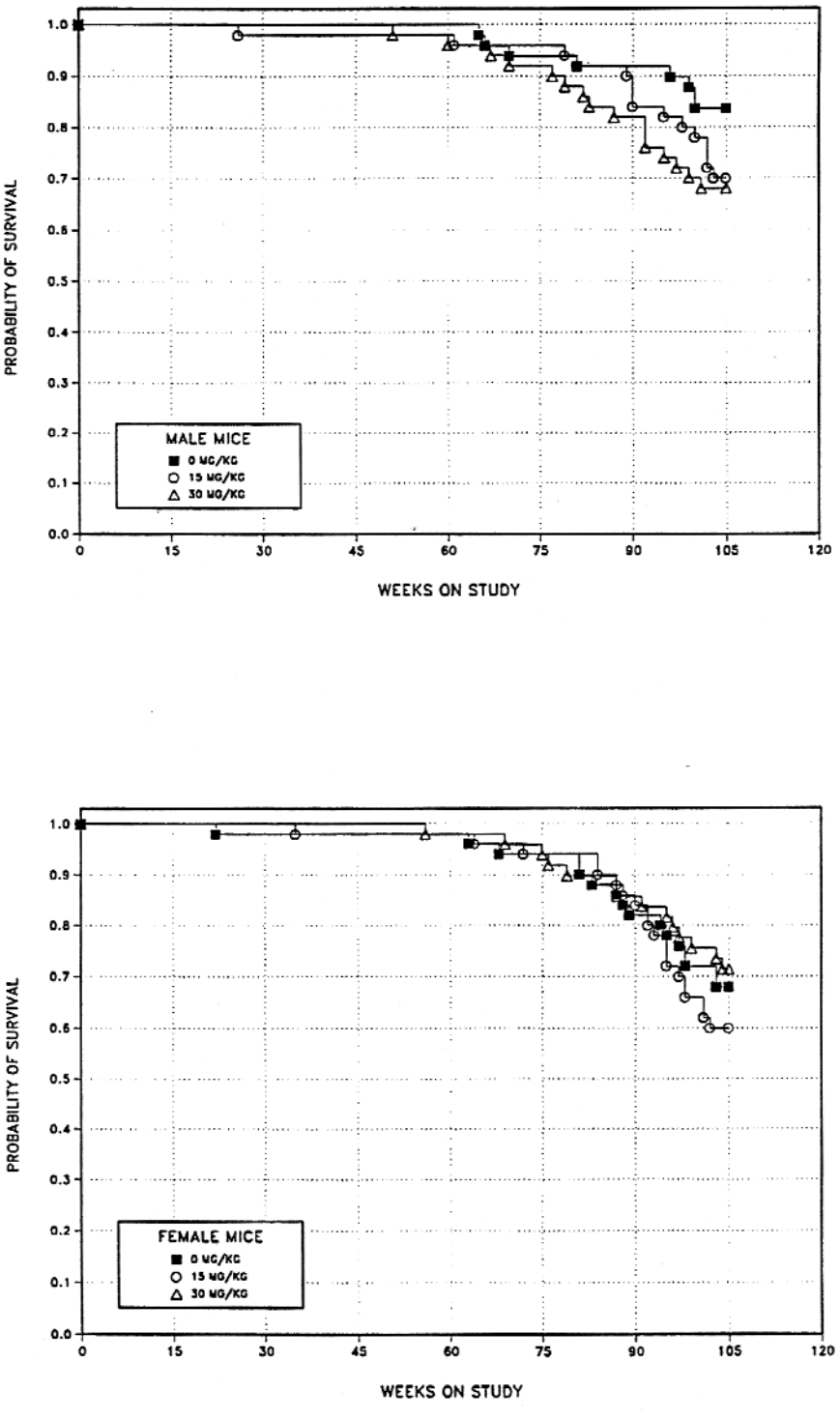


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Oleic Acid Diethanolamine Condensate Dermally for 2 Years

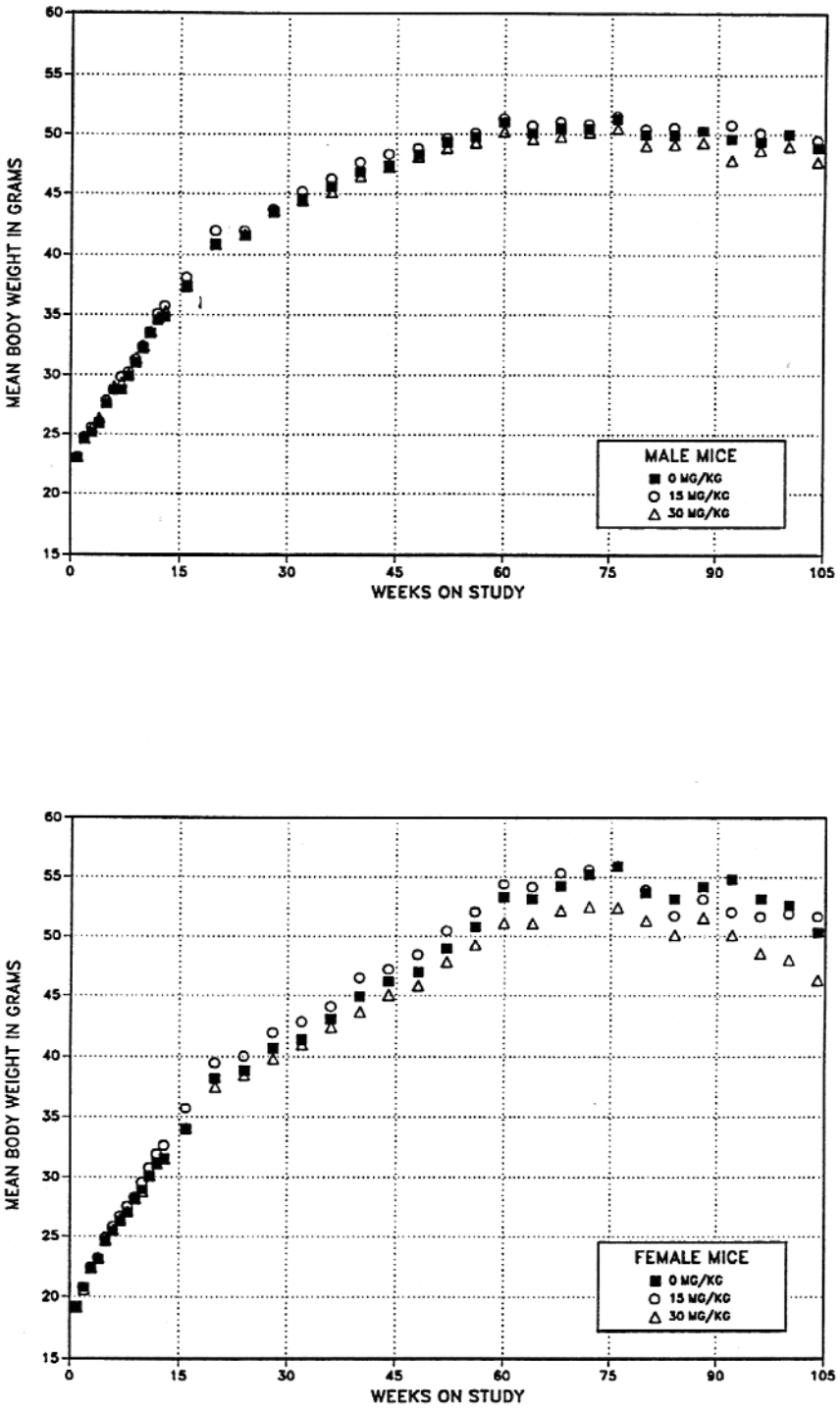


FIGURE 4
Growth Curves for Male and Female Mice
Administered Oleic Acid Diethanolamine Condensate Dermally for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

Weeks on Study	Vehicle Control		15 mg/kg			30 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
1	23.0	55	23.1	100	55	23.1	100	55
2	24.5	55	24.7	101	55	24.6	100	55
3	25.1	55	25.6	102	55	25.5	102	55
4	25.9	55	26.1	101	55	26.4	102	55
5	27.6	55	27.9	101	55	27.9	101	55
6	28.7	55	28.8	100	55	29.0	101	55
7	28.8	54	29.8	104	55	29.4	102	55
8	29.9	54	30.3	101	55	30.1	101	55
9	31.0	54	31.3	101	55	31.4	101	55
10	32.2	54	32.4	101	55	32.4	101	55
11	33.5	54	33.5	100	55	33.6	100	55
12	34.5	54	35.1	102	55	34.7	101	55
13	34.8	54	35.7	103	55	35.3	101	55
16[a]	37.4	49	38.1	102	50	37.4	100	50
20	40.9	49	42.0	103	50	40.8	100	50
24	41.5	49	41.9	101	50	41.7	101	50
28	43.5	49	43.7	101	49	43.6	100	50
32	44.6	49	45.2	101	49	44.5	100	50
36	45.6	49	46.3	102	49	45.2	99	50
40	46.8	49	47.7	102	49	46.5	99	50
44	47.3	49	48.3	102	49	47.3	100	50
48	48.3	49	48.8	101	49	48.1	100	50
52	49.3	49	49.7	101	49	48.8	99	49
56	49.7	49	50.1	101	49	49.3	99	49
60	51.0	49	51.3	101	49	50.2	98	49
64	50.0	49	50.7	101	48	49.6	99	48
68	50.5	47	51.0	101	48	49.8	99	47
72	50.5	46	50.9	101	48	50.2	99	46
76	51.3	46	51.5	100	48	50.5	98	46
80	50.0	46	50.5	101	47	49.1	98	44
84	49.9	45	50.6	101	46	49.2	99	42
88	50.3	45	50.3	100	46	49.3	98	41
92	49.6	45	50.8	102	42	47.8	96	41
96	49.4	45	50.1	101	41	48.7	99	37
100	50.0	43	50.0	100	40	49.0	98	35
104	48.8	41	49.5	101	35	47.7	98	34
Mean for weeks								
1-13	29.2		29.6	101		29.5	101	
14-52	44.5		45.2	102		44.4	100	
53-104	50.1		50.6	101		49.3	98	

[a] Interim evaluation occurred during week 13.

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

Weeks on Study	Vehicle Control		15 mg/kg			30 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
1	19.2	55	19.2	100	55	19.1	100	55
2	20.7	55	20.8	101	55	20.6	100	55
3	22.3	55	22.4	100	55	22.4	100	55
4	23.1	55	23.2	100	55	23.2	100	55
5	24.6	55	24.9	101	55	24.7	100	55
6	25.4	55	25.8	102	55	25.5	100	55
7	26.2	55	26.7	102	55	26.5	101	55
8	27.0	55	27.5	102	55	27.1	100	55
9	28.1	55	28.3	101	55	28.2	100	55
10	28.9	55	29.6	102	55	28.8	100	55
11	30.1	55	30.8	102	55	30.1	100	55
12	31.2	55	31.9	102	55	31.1	100	55
13	31.6	55	32.6	103	55	31.5	100	55
16[a]	34.0	50	35.7	105	50	34.1	100	50
20	38.2	50	39.5	103	50	37.5	98	50
24	38.8	49	40.0	103	50	38.5	99	50
28	40.6	49	41.9	103	50	39.8	98	50
32	41.3	49	42.9	104	50	41.0	99	50
36	43.0	49	44.1	103	49	42.4	99	50
40	44.9	49	46.5	104	49	43.7	97	50
44	46.2	49	47.2	102	49	45.1	98	50
48	47.0	49	48.5	103	49	45.9	98	50
52	49.0	49	50.5	103	49	47.9	98	50
56	50.8	49	52.1	103	49	49.3	97	49
60	53.3	49	54.4	102	49	51.1	96	48
64	53.2	48	54.2	102	49	51.1	96	48
68	54.3	48	55.3	102	48	52.2	96	48
72	55.2	47	55.6	101	48	52.5	95	47
76	55.9	47	56.0	100	47	52.5	94	46
80	53.7	47	54.0	101	47	51.4	96	44
84	53.1	44	51.8	98	47	50.1	94	44
88	54.2	43	53.2	98	44	51.6	95	42
92	54.8	41	52.0	95	42	50.1	91	41
96	53.2	39	51.7	97	36	48.6	91	40
100	52.6	36	51.9	99	33	48.0	91	37
104	50.3	34	51.7	103	30	46.3	92	36
Mean for weeks								
1-13	26.0		26.4	102		26.1	100	
14-52	42.3		43.7	103		41.6	98	
53-104	53.4		53.4	100		50.4	94	

[a] Interim evaluation occurred during week 13.

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant lymphoma and neoplasms and nonneoplastic lesions of the skin. 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 C for male mice and Appendix D for female mice.

Malignant Lymphoma: The incidence of malignant lymphoma in female mice increased with increasing dose and was significantly increased in the 30 mg/kg group compared to the vehicle controls (vehicle control, 3/50; 15 mg/kg, 9/50; 30 mg/kg 11/50; Table D3). The historical control incidence of malignant lymphoma in dermal studies using ethanol as a vehicle is 15/102 for female mice. In studies of diethanolamine and other diethanolamine condensates, the incidences in control groups of female mice were 12/50 (24%) for diethanolamine (NTP, 1999a), 13/50 (26%) for coconut oil acid diethanolamine condensate (NTP, 1999b), and 9/50 (18%) for lauric acid diethanolamine condensate (NTP, 1999c). In this study, the incidence in the 30 mg/kg group (11/50; 22%) was similar to the incidences observed in the other dermal studies with ethanol as the vehicle; the incidence in the vehicle control group (3/50; 6%) was much lower.

Skin: In general, neoplasms of the skin at the site of application occurred only in females, were few in number, and did not follow a dose-related pattern of incidence. There was one fibrosarcoma at the site of application in a vehicle control female and two fibrosarcomas at the site of application in the 15 mg/kg female group (Table D1).

The incidences of epidermal hyperplasia and sebaceous gland hyperplasia in all male and female dosed groups were significantly increased relative to the vehicle controls at the 3-month interim evaluation and at 2 years (Tables 14, C4, and D4). The incidences of hyperkeratosis were increased relative to the vehicle controls in dosed males at 3 months and in dosed males and females at 2 years. At 3 months and at 2 years, the incidences of parakeratosis in 30 mg/kg males were significantly greater than those in the vehicle control group. At 2 years, the lesions were more severe in the 30 mg/kg groups than in the 15 mg/kg or vehicle control groups, but all were minimal to mild in severity. These lesions were slightly more severe in females than in males. The incidences of chronic active dermal inflammation of the dermis in all male and female dosed groups were significantly increased relative to the vehicle controls at the 3-month interim evaluation and at 2 years. At 2 years, the incidences of ulcer in 30 mg/kg males and of exudate in 30 mg/kg males and females were increased relative to the vehicle controls. Epidermal hyperplasia and sebaceous gland hyperplasia usually occurred simultaneously.

GENETIC TOXICOLOGY

Oleic acid diethanolamine condensate (0.1 to 200 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation enzymes (Table E1). In addition, no induction of trifluorothymidine resistance was noted in L5178Y mouse lymphoma cells treated with oleic acid diethanolamine condensate in the presence or absence of S9 metabolic activation (Table E2).

TABLE 14
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
3-Month Interim Evaluation			
Number Examined Microscopically	5	5	5
Epidermal Hyperplasia[a]	0	5** (1.2)[b]	5** (2.0)
Sebaceous Gland, Hyperplasia	0	5** (1.0)	5** (1.0)
Hyperkeratosis	0	4* (1.0)	4* (1.0)
Parakeratosis	0	1 (1.0)	4* (1.0)
Dermal Inflammation, Chronic Active	0	5** (1.0)	5** (1.6)
Ulcer	0	0	1 (1.0)
2-Year Study			
Number Examined Microscopically	49	50	50
Epidermal Hyperplasia	1 (1.0)	40** (1.3)	47** (2.1)
Sebaceous Gland, Hyperplasia	1 (1.0)	21** (1.2)	34** (1.5)
Hyperkeratosis	1 (1.0)	38** (1.0)	37** (1.3)
Parakeratosis	0	2 (1.0)	8** (1.3)
Dermal Inflammation, Chronic Active	0	34** (1.2)	50** (1.7)
Exudate	1 (1.0)	3 (1.0)	9** (1.4)
Ulcer	0	0	7** (2.3)
Female			
3-Month Interim Evaluation			
Number Examined Microscopically	5	5	5
Epidermal Hyperplasia	0	5** (1.0)	4* (1.0)
Sebaceous Gland, Hyperplasia	0	5** (1.0)	5** (1.0)
Hyperkeratosis	0	2 (1.0)	3 (1.0)
Dermal Inflammation, Chronic Active	0	4* (1.0)	4* (1.0)
2-Year Study			
Number Examined Microscopically	50	50	50
Epidermal Hyperplasia	0	43** (1.3)	50** (1.9)
Sebaceous Gland, Hyperplasia	0	39** (1.2)	46** (1.6)
Hyperkeratosis	0	36** (1.1)	42** (1.4)
Parakeratosis	0	0	4 (2.3)
Dermal Inflammation, Chronic Active	0	40** (1.1)	49** (2.3)
Exudate	0	0	6* (1.7)

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

DISCUSSION AND CONCLUSIONS

Oleic acid diethanolamine condensate is a member of a group of fatty acid diethanolamine condensates widely used as emollients, thickeners, and foam stabilizers in cosmetics, shampoos, conditioners, and hair dyes. Because of the extensive human exposure to these compounds and the absence of information concerning the consequences of long-term exposure, oleic acid diethanolamine condensate, lauric acid diethanolamine condensate, and coconut oil acid diethanolamine condensate were selected for evaluation of carcinogenic potential as representatives of this class of compounds. Because diethanolamine is used in the synthesis of all the diethanolamides, and free diethanolamine is present at varying concentrations as a contaminant of commercial diethanolamide preparations, the carcinogenic potential of diethanolamine was also evaluated. The primary route of human exposure to products containing diethanolamides is by contact with skin. Therefore, this series of studies was conducted by dermal administration.

Dose selection for the 2-year studies in both rats and mice was based primarily on the incidences and severities of skin lesions observed at the site of application during the 13-week studies. A clear pattern of dose response was observed in rats. In general, doses of 200 and 400 mg/kg were associated with reduced mean body weights and high incidences of lesions of the skin at the site of application in male and female rats. These doses were considered inappropriate for a 2-year study. In the 100 mg/kg groups of rats, the incidences and severities of skin lesions were less than those observed in the 200 or 400 mg/kg groups. The severities of skin lesions at the site of application in rats administered 200 or 400 mg/kg differed very little and in general were only slightly greater than those in groups administered 100 mg/kg. Therefore, it was considered unlikely that these lesions would progress and become life threatening over a 2-year period. Based on these results, 100 mg/kg was selected as the high dose for rats in the 2-year study. In groups administered 50 mg/kg, the incidences of skin lesions diminished considerably compared to the 100 mg/kg group, and the severities were minimal. Therefore, 50 mg/kg was selected as the low dose.

All doses of oleic acid diethanolamine condensate used during the 13-week mouse study were considered inappropriate for a 2-year study. Groups of mice administered 100 mg/kg or greater exhibited high incidences of skin lesions at the site of application. Although the severities of parakeratosis and suppurative inflammation increased with increasing dose in groups administered doses greater than 100 mg/kg, the severities of other lesions generally seemed to plateau, increasing only slightly in groups administered 100 to 800 mg/kg in spite of the eightfold increase in dose. Therefore, above 100 mg/kg, increasing the dose did not produce a proportional increase in skin response. The incidences of skin lesions in groups administered 50 mg/kg were slightly less than those observed in groups administered 100 mg/kg, and the severities of lesions in the 50 mg/kg groups were less than those observed in the 100 mg/kg groups. However, the slight reduction in incidences and lower severities observed in 50 mg/kg groups indicated that 50 mg/kg was within a dose range in which skin response at the site of application exhibited a greater dose dependency. Therefore, at doses below 50 mg/kg, a proportional reduction in incidences and severities of skin lesions at the site of application would be expected. Accordingly, a high dose of 30 mg/kg, approximately one half of 50 mg/kg, and a low dose of 15 mg/kg, approximately one fourth of 50 mg/kg, were selected for the 2-year mouse study. In order to confirm that these doses were appropriate for a 2-year study, five additional animals were included in each group of mice for interim evaluation after 3 months of dosing.

In rats, lesions at the site of application at the end of the 2-year study in both the 50 and 100 mg/kg groups were generally of mild severity compared to the minimal to mild severities observed in the 100 mg/kg groups during the 13-week study. The severities of skin lesions at the site of application observed at the 3-month interim sacrifice in mice were very similar to the severities of comparable lesions observed at the end of the 2-year study. Increased incidences of ulceration at the site of application were the major difference between the response observed in the 13-week studies and that observed at the end of the 2-year

studies in both rats and mice. The incidences of ulceration were particularly high in female rats; however, the ulcers were very small, focal microscopic lesions too small to be seen grossly and consisted of loss of epidermis. In most instances the underlying dermis had only a minimal to mild inflammatory reaction. Therefore, in both rats and mice, the severities of skin lesions that occurred in the 2-year studies did not progress significantly beyond the severities observed in the 13-week studies.

No neoplasms were associated with administration of oleic acid diethanolamine condensate in rats or mice. The incidence of interstitial cell adenoma of the testis increased with increasing dose in male rats and was significantly increased in 100 mg/kg males. The historical control incidence for this neoplasm in dermal studies with ethanol as a vehicle is 66/102; however, this is based on only two other studies, one with a control rate of 24/50 (48%), the same as in the present study, and one with a control rate of 42/52 (81%). The incidence in the 100 mg/kg group, 37/50 (74%), is within the historical control range. In the companion studies of other diethanolamides, the control rates for interstitial cell adenoma in male rats were 32/50 (64%) for diethanolamine (NTP, 1999a), 23/50 (46%) for coconut oil acid diethanolamine condensate (NTP, 1999b), and 20/50 (40%) for lauric acid diethanolamine condensate (NTP, 1999c). Because this is a very common neoplasm in aging male F344/N rats and because control rates exhibit considerable variability, the increase in the 100 mg/kg group was not considered to be associated with oleic acid diethanolamine condensate administration.

The incidence of malignant lymphoma in female mice increased with increasing dose and was significantly increased in the 30 mg/kg group. The historical control incidence of malignant lymphoma in dermal studies with ethanol as a vehicle is 15/102 for female mice. In companion studies of diethanolamine and other diethanolamine condensates, the incidence in control groups of female mice was 12/50 (24%) for diethanolamine (NTP, 1999a) 13/50 (26%) for coconut oil acid diethanolamide condensate (NTP, 1999b), and 9/50 (18%) for lauric acid diethanolamine condensate (NTP, 1999c). In the present study, the incidence in the 30 mg/kg group (11/50; 22%) was well within the control range for this neoplasm in other dermal studies with ethanol as the vehicle, but the incidence in the control group (3/50; 6%) was much lower. Malignant lymphoma is a common neoplasm in aging female $B6C3F_1$ mice, and the increase observed in the present study is a consequence of the unusually low incidence of this neoplasm in control female mice and is not associated with administration of oleic acid diethanolamine condensate.

The results of the present study fit into a pattern of response observed in the 2-year studies of diethanolamine (NTP, 1999a) and the other diethanolamine condensates (NTP, 1999b,c). 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 of renal tubule neoplasms in male mice. The comparison also reveals a clear difference between male and female mice in their response to diethanolamine exposure. These responses were not observed in the present study because mice in this study received lower doses of diethanolamide (and contaminating diethanolamine) than mice in the lauric acid diethanolamine condensate or coconut oil acid diethanolamine condensate studies.

In the lauric acid diethanolamine condensate and coconut oil acid diethanolamine condensate studies, mice received 100 or 200 mg/kg of the diethanolamide. Coconut oil acid diethanolamine condensate contained 18.2% free diethanolamine by weight; therefore, mice in that study were exposed to 18.2 or 36.4 mg/kg free diethanolamine. Lauric acid diethanolamine condensate contained 0.83% free diethanolamine by weight; mice in that study were exposed to 8.3 or 1.66 mg/kg free diethanolamine. The oleic acid diethanolamine condensate used in this study contained 0.19% free diethanolamine by weight; however, mice were given doses of only 15 or 30 mg/kg oleic acid diethanolamide and therefore only 0.028 or 0.056 mg/kg free diethanolamine.

Absorption, distribution, and metabolism studies of lauric acid diethanolamine condensate revealed that this diethanolamide is well absorbed after dermal or oral administration and eliminated primarily in the urine as the half amides of succinic and adipic acid (Mathews *et al.*, 1996). No parent diethanolamide and no diethanolamine or diethanolamine-derived metabolites were detected in the urine even after oral doses of 1,000 mg/kg. This suggests that lauric acid diethanolamine condensate metabolism involves ω-hydroxylation followed by β-oxidation to half

amides that are eliminated in urine. Therefore, no additional bioavailable diethanolamine was released as a result of metabolic cleavage of the amide linkage, specifically for lauric acid diethanolamine condensate, and quite likely for coconut oil acid diethanolamine condensate and oleic acid diethanolamine condensate.

To quantify the association between the incidence of hepatocellular neoplasms and diethanolamine concentration, a logistic regression model was fitted to individual animal neoplasm incidence and survival data from the studies of diethanolamine and the three diethanolamides. The model predicts the incidence of hepatocellular neoplasms as a function of diethanolamine dose (mg/kg) and survival (days). 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 response in the diethanolamine study and the three diethanolamine condensate studies is determined primarily by the concentration of free diethanolamine. Therefore, the negative response observed in the present study fits into the overall response pattern for the other diethanolamides.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of oleic acid diethanolamine condensate in male or female F344/N rats administered 50 or 100 mg/kg or in male or female B6C3F$_1$ mice administered 15 or 30 mg/kg.

Dermal administration of oleic acid diethanolamine condensate to male and female rats was associated with epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, parakeratosis, chronic active inflammation of the dermis, and ulcer of the skin at the site of application. Dermal administration of oleic acid diethanolamine condensate to mice was associated with epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, chronic active inflammation of the dermis, and exudate of the skin at the site of application in males and females and parakeratosis and ulceration of the skin at the site of application in males.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Report Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

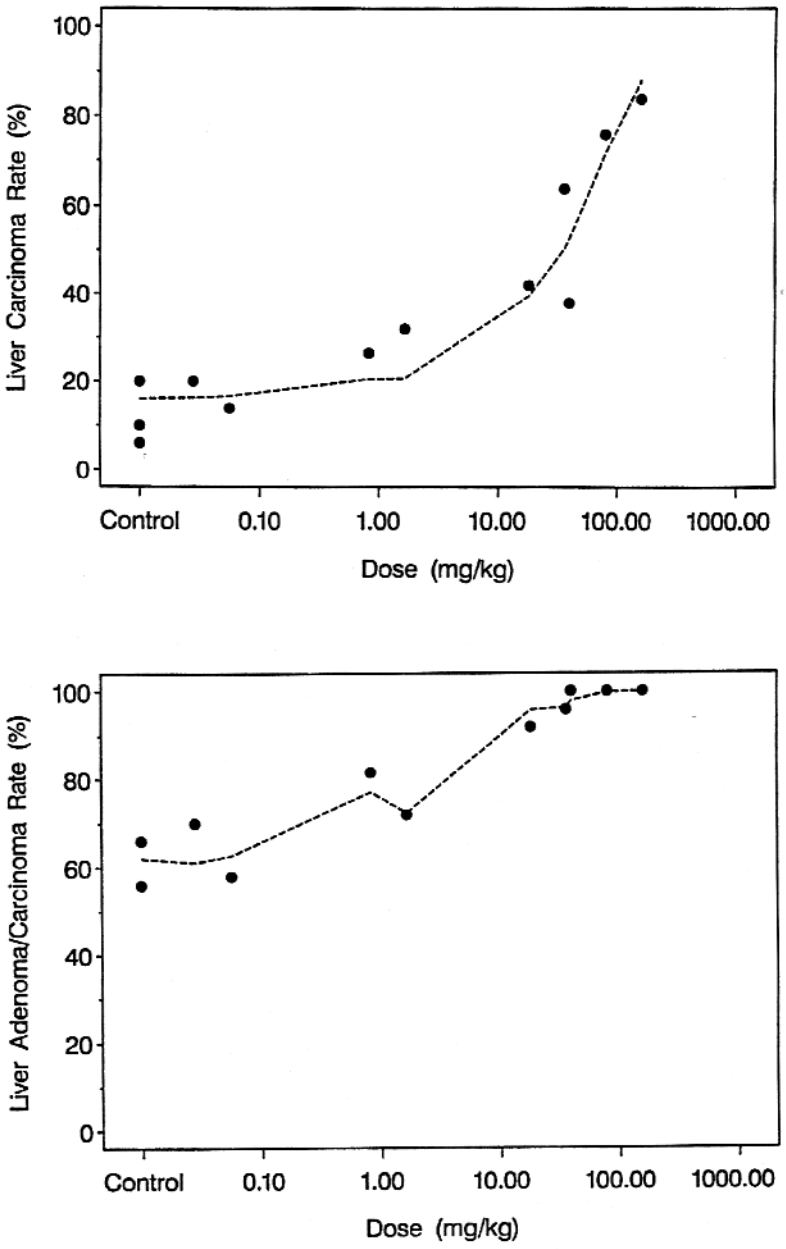

FIGURE 5
Observed and Predicted Liver Neoplasm Incidences in Female B6C3F$_1$ Mice as a Function of Dose and Survival (•=Observed, ----=Predicted). Predicted rates are based on the logistic regression model, P=1/[1+exp(T)], where P is the probability of observing a neoplasm. For carcinoma, T=3.2425 – 0.00226S, and for adenoma/carcinoma, T=6.3820 – 0.6822D – 0.0097S, where D=dose$^{1/2}$ in mg diethanolamine/kg body weight and S=survival in days.

REFERENCES

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Bailer, A.J., and Portier, C.J. (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* **44**, 417-431.

Bieler, G.S., and Williams, R.L. (1993). Ratio of estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics* **49**, 793-801.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Caspary, W.J., Lee, Y.J., Poulton, S., Myhr, B.C., Mitchell, A.D., and Rudd, C.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Quality-control guidelines and response categories. *Environ. Mol. Mutagen.* **12** (Suppl. 13), 19-36.

Code of Federal Regulations (CFR) **21**, Part 58.

Cosmetic, Toiletry and Fragrance Association (CTFA) (1985). Final report of the safety assessment for cocamide DEA, lauramide DEA, linoleamide DEA, oleamide DEA. June 26, 1985.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology. Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Dixon, W.J., and Massey, F.J., Jr. (1951). *Introduction to Statistical Analysis*, 1st ed., pp. 145-147. McGraw-Hill Book Company, Inc., New York.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *JNCI* **62**, 957-974.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

de Kok, T.M.C.M., ten Vaarwerk, F., Zwingman, I., van Maanen, J.M.S., and Kleinjans, J.C.S. (1994). Peroxidation of linoleic, arachidonic and oleic acid in relation to the induction of oxidative DNA damage and cytogenetic effects. *Carcinogenesis* **15**, 1399-1404.

Lehninger, A.L. (1982). The oxidation of fatty acids in animal tissues. In *Principles of Biochemistry*, pp. 511-530. Worth Publishers, Inc., New York.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

Matthews, J.M., Decosta, K., and Thomas, B.F. (1996). Lauramide diethanolamine absorption, metabolism, and disposition in rats and mice after oral, intravenous, and dermal administration. *Drug Metab. Dispos.* **24**, 702-710.

Midwest Research Institute (MRI) (1978). Preliminary report on oleic acid diethanolamine condensate, 18 September 1978. Midwest Research Institute, Kansas City, MO.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Morrison, D.F. (1976). *Multivariate Statistical Methods*, 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., and Zeiger, E. (1986). *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutagen.* **8** (Suppl. 7), 1-119.

Myhr, B., Bowers, L., and Caspary, W.J. (1985). Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. In *Progress in Mutation Research: Evaluation of Short-term Tests for Carcinogens; Report of the International Programme on Chemical Safety s Collaborative Study on In vitro Assays* (J. Ashby, F.J. de Serres, M. Draper, M. Ishidate, Jr., B.H. Margolin, B.E. Matter, and M.D. Shelby, Eds.), Vol. 5, pp. 555-568. Elsevier Science Publishers, Amsterdam.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1990). National Occupational Exposure Survey (1981-1983), unpublished provisional data as of July 1, 1990. NIOSH, Cincinnati, OH.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, NIH, Bethesda, MD.

National Toxicology Program (NTP) (1987). Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluations in Toxicity Testing for Rats and Mice. 10/31/82 version (updated December 1987). Research Triangle Park, NC.

National Toxicology Program (NTP) (1995). Toxicology and Carcinogenesis Studies of Benzethonium Chloride (CAS No. 121-54-0) in F344/N Rats and $B6C3F_1$ Mice (Dermal Studies). Technical Report Series No. 438. NIH Publication No. 95-3169. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1998). Toxicology and Carcinogenesis Studies of Technical Grade Sodium Xylenesulfonate (CAS No. 1300-72-7) in F344/N Rats and $B6C3F_1$ Mice (Dermal Studies). Technical Report Series No. 464. NIH Publication No. 98-3380. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1999a). Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and $B6C3F_1$ Mice (Dermal Studies). Technical Report Series No. 478. NIH Publication No. 99-3968. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1999b). Toxicology and Carcinogenesis Studies of Coconut Oil Acid Diethanolamine Condensate (CAS No. 68603-42-9) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). Technical Report Series No. 479. NIH Publication No. 99-3969. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1999c). Toxicology and Carcinogenesis Studies of Lauric Acid Diethanolamine Condensate (CAS No. 120-40-1) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). Technical Report Series No. 480. NIH Publication No. 99-3970. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Piegorsch, W.W., and Bailer, A.J. (1997). *Statistics for Environmental Biology and Toxicology*, Section 6.3.2. Chapman and Hall, London.

Portier, C.J., and Bailer, A.J. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam. Appl. Toxicol.* **12**, 731-737.

Portier, C.J., Hedges, J.C., and Hoel, D.G. (1986). Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res.* **46**, 4372-4378.

Record, I.R., Konstantinopoulos, M., and Nestel, P.J. (1992). A comparative study of micronucleus frequency in peripheral blood lymphocytes of human subjects given dietary *cis*, *trans* and saturated fat. *Food Chem. Toxicol.* **30**, 585-588.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988). *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. Mol. Mutagen.* **11** (Suppl. 12), 1-158.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	26	30	24
Natural deaths	16	10	12
Survivors			
Terminal sacrifice	8	10	14
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, cecum	(38)	(41)	(40)
Intestine small, duodenum	(50)	(50)	(50)
Intestine small, jejunum	(42)	(45)	(43)
Carcinoma			1 (2%)
Leiomyosarcoma			1 (2%)
Intestine small, ileum	(41)	(45)	(45)
Liver	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)		
Hepatocellular adenoma		1 (2%)	
Mesentery	(5)	(7)	(3)
Oral mucosa	(1)		
Squamous cell papilloma	1 (100%)		
Pancreas	(50)	(50)	(50)
Acinus, adenoma			1 (2%)
Salivary glands	(50)	(50)	(50)
Carcinoma		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Squamous cell papilloma			1 (2%)
Stomach, glandular	(50)	(49)	(50)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Heart	(50)	(49)	(50)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma complex			1 (2%)
Pheochromocytoma benign	8 (16%)	3 (6%)	3 (6%)
Bilateral, pheochromocytoma benign	4 (8%)	3 (6%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)		3 (6%)
Carcinoma	2 (4%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(49)
Pars distalis, adenoma	37 (74%)	38 (76%)	39 (80%)
Pars distalis, adenoma, multiple	1 (2%)		1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System (continued)			
Thyroid gland	(50)	(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)
C-cell, adenoma	2 (4%)	5 (10%)	6 (12%)
C-cell, carcinoma	2 (4%)	1 (2%)	1 (2%)
Follicular cell, adenoma		4 (8%)	1 (2%)
Follicular cell, carcinoma		2 (4%)	1 (2%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)
Carcinoma			1 (2%)
Prostate	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)
Testes	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	14 (28%)	16 (32%)	21 (42%)
Interstitial cell, adenoma	10 (20%)	14 (28%)	16 (32%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Lymph node	(2)		
Lymph node, mandibular	(49)	(49)	(49)
Lymph node, mesenteric	(49)	(48)	(50)
Spleen	(50)	(50)	(50)
Thymus	(45)	(42)	(44)
Integumentary System			
Mammary gland	(49)	(49)	(49)
Carcinoma	1 (2%)		
Fibroadenoma	3 (6%)		1 (2%)
Skin	(50)	(50)	(50)
Basal cell adenoma	1 (2%)		
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Keratoacanthoma	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)
Subcutaneous tissue, lipoma	1 (2%)		
Subcutaneous tissue, skin, site of application, fibroma	1 (2%)		
Subcutaneous tissue, skin, site of application, fibrosarcoma		1 (2%)	1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Musculoskeletal System			
Bone	(50)	(49)	(50)
Vertebra, chordoma			1 (2%)
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	
Hemangiosarcoma, metastatic, skin	1 (2%)		
Special Senses System			
Zymbal's gland	(1)		
Carcinoma	1 (100%)		
Urinary System			
Kidney	(50)	(50)	(50)
Renal tubule, adenoma	3 (6%)	4 (8%)	1 (2%)
Renal tubule, carcinoma	1 (2%)		
Urinary bladder	(49)	(50)	(50)
Papilloma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
Leukemia granulocytic	1 (2%)		
Leukemia mononuclear	14 (28%)	13 (26%)	13 (26%)
Lymphoma malignant	1 (2%)		1 (2%)
Mesothelioma malignant	2 (4%)	1 (2%)	3 (6%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	49	48	50
Total primary neoplasms	117	114	127
Total animals with benign neoplasms	47	47	49
Total benign neoplasms	90	91	99
Total animals with malignant neoplasms	21	18	22
Total malignant neoplasms	27	23	28
Total animals with metastatic neoplasms	1		
Total metastatic neoplasms	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 Oleic Acid Diethanolamine Condensate: Vehicle Control

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

Number of Days on Study	6 3 8	6 4 7	6 5 3	6 5 3	6 5 4	6 5 4	6 5 4	6 5 9	6 7 4	6 7 8	6 9 4	6 9 9	7 0 0	7 0 0	7 0 6	7 0 7	7 1 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	0 4 6	0 4 4	0 0 1	0 4 9	0 1 0	0 2 7	0 3 0	0 3 7	0 3 3	0 3 8	0 4 8	0 3 1	0 1 1	0 5 0	0 3 6	0 2 1	0 1 7	0 0 4	0 0 7	0 1 9	0 2 0	0 2 2	0 2 4	0 3 4	0 3 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	38
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									1
Mesentery														+	+								+		5
Oral mucosa																									1
Squamous cell papilloma																									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
Pheochromocytoma benign						X	X	X	X		X				X								X		8
Bilateral, pheochromocytoma benign	X													X		X				X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Carcinoma																X							X		2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X	37
Pars distalis, adenoma, multiple								X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X										X														2
C-cell, carcinoma											X											X			2
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X				X		X					X	X	X	X		X			X	14
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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	2 9 3	4 4 0	4 4 0	4 6 9	4 7 3	4 9 5	5 0 6	5 1 7	5 3 0	5 4 2	5 4 9	5 7 1	5 7 4	5 8 0	5 9 8	6 0 3	6 0 8	6 1 3	6 1 4	6 1 8	6 2 3	6 3 4	6 3 7	6 3 8	6 3 8
Carcass ID Number	0 4 3	0 2 3	0 3 9	0 0 3	0 0 2	0 1 5	0 3 8	1 1 3	1 1 4	1 1 6	3 2 2	4 1 1	4 2 2	4 4 5	1 2 2	0 5 5	2 0 8	0 0 6	2 2 9	2 6 6	4 0 0	4 4 7	0 1 9	1 8 8	2 2 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																	+				+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																			X						
Hemangiosarcoma			X																						
Keratoacanthoma																			X						
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, lipoma							X																		
Subcutaneous tissue, skin, site of application, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Zymbal's gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma											X														
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic																							X		
Leukemia mononuclear	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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	6 3 8	6 4 7	6 5 3	6 5 3	6 5 4	6 5 4	6 5 4	6 5 9	6 7 4	6 7 8	6 9 4	6 9 9	7 0 0	7 0 0	7 0 6	7 0 7	7 1 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	0 4 6	0 4 4	0 0 1	0 4 9	0 1 0	0 2 7	0 3 0	0 3 7	0 3 3	0 3 8	0 4 8	0 4 8	0 3 1	0 1 1	0 1 0	0 3 6	0 2 1	0 1 7	0 0 4	0 0 7	0 1 9	0 2 0	0 2 2	0 2 4	0 3 4	0 3 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																							X			1
Fibroadenoma																						X			X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Hemangiosarcoma																										1
Keratoacanthoma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, skin, site of application, fibroma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+																				2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma					X						X				X											3
Renal tubule, carcinoma																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Leukemia mononuclear			X	X											X			X	X	X		X		X		14
Lymphoma malignant																										1
Mesothelioma malignant																									X	2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	6 3 6	6 3 7	6 3 8	6 3 8	6 5 3	6 5 3	6 5 4	6 5 9	6 6 8	6 7 4	6 9 6	6 9 9	7 0 6	7 0 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	0 6 5	0 8 3	0 8 8	0 8 9	0 5 5	0 8 5	0 9 0	0 5 3	0 6 6	0 8 2	0 9 7	0 7 8	0 5 7	0 5 1	0 9 2	0 5 2	0 6 2	0 6 3	0 7 2	0 7 9	0 8 6	0 9 1	0 9 3	0 9 4	0 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery						+			+					+	+					+						7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X							X			3
Bilateral, pheochromocytoma benign					X												X									3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X	X	X		X	X		X		X		X		X	X	X	X	X	X	X	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X		X		X																				5
C-cell, carcinoma																				X						1
Follicular cell, adenoma										X											X					4
Follicular cell, carcinoma																		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	X		X	X	X				16
Interstitial cell, adenoma						X				X		X											X	X	X	14

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	6 3 6	6 3 7	6 3 8	6 3 8	6 5 3	6 5 3	6 5 4	6 5 9	6 6 8	6 7 4	6 9 6	6 9 9	7 0 6	7 0 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	0 6 5	0 8 3	0 8 8	0 8 9	0 5 5	0 8 5	0 9 0	0 5 3	0 6 6	0 8 2	0 9 7	0 7 8	0 5 7	0 5 1	0 9 2	0 5 2	0 6 2	0 6 3	0 7 2	0 7 9	0 8 6	0 9 1	0 9 3	0 9 4	0 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Subcutaneous tissue, fibroma								X																		1
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, skin, site of application, fibrosarcoma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					1
Alveolar/bronchiolar carcinoma																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland														+												1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma							X			X									X							4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear									X	X				X		X			X		X		X		X	13
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	4 8 2	4 9 7	5 0 2	5 2 6	5 2 9	5 3 2	5 3 5	5 4 9	5 5 4	5 7 6	5 8 0	5 8 0	5 9 1	6 1 1	6 1 8	6 2 8	6 3 1	6 3 6	6 3 8	6 3 8	6 3 8	6 3 8	6 4 4	6 4 7	6 6 1
Carcass ID Number	1 0 9	1 0 7	1 4 5	1 3 8	1 1 9	1 1 6	1 3 7	1 1 5	1 2 8	1 0 5	1 0 3	1 4 3	1 1 2	1 4 8	1 3 1	1 2 6	1 4 4	1 3 2	1 2 3	1 2 4	1 2 7	1 4 6	1 3 6	1 0 2	1 3 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	A	A	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+
Carcinoma																									
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																+	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																								X	
Pheochromocytoma benign																									X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X		X	X	X	X	X			X		X	X	X		X		X	X	X	X	X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																					X				
C-cell, carcinoma																				X					
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	6 7 4	6 7 6	6 7 6	6 7 7	6 9 6	7 0 3	7 0 3	7 1 0	7 1 3	7 2 3	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 4 9	1 0 4	1 3 5	1 2 5	1 4 7	1 2 1	1 3 4	1 3 3	1 3 0 1	1 0 6	1 1 7	1 0 8	1 1 0	1 1 1	1 1 3	1 1 4	1 1 8	1 2 0	1 2 2	1 2 9	1 3 9	1 4 0	1 4 1	1 4 2	1 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma																X										1
Leiomyosarcoma										X																1
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+																3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma													X													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma						X																				1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex																										1
Pheochromocytoma benign																				X		X				3
Bilateral, pheochromocytoma benign											X					X								X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X								X													3
Carcinoma																						X				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			X	39
Pars distalis, adenoma, multiple																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma										X																1
C-cell, adenoma			X								X						X	X				X				6
C-cell, carcinoma																										1
Follicular cell, adenoma																				X						1
Follicular cell, carcinoma																X										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	482	497	502	526	529	532	535	549	554	576	580	580	591	611	618	628	631	636	638	638	638	644	647	661
Carcass ID Number	10909	10907	10445	10938	10919	10916	10937	10915	10828	10905	10903	10443	10912	10848	10931	10826	10944	10932	10823	10824	10827	10946	10936	10930
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma				X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X												X								
Interstitial cell, adenoma					X	X		X		X	X		X		X		X	X		X	X	X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																								
Subcutaneous tissue, skin, site of application, fibrosarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, chordoma					X																			
Skeletal muscle																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X		X		X		X		X			X		
Lymphoma malignant																								
Mesothelioma malignant																X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	6 7 4	6 7 6	6 7 6	6 7 7	6 9 6	7 0 3	7 0 3	7 1 0	7 1 3	7 2 3	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 4 9	1 0 4	1 3 5	1 2 5	1 4 7	1 2 1	1 3 4	1 3 3	1 3 0	1 0 6	1 1 7	1 0 8	1 1 0	1 1 1	1 1 3	1 1 4	1 1 8	1 2 0	1 2 2	1 2 9	1 3 9	1 4 0	1 4 1	1 4 2	1 5 0	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X			X	X	X	X	X	X		X	X	X	X		X	X	X		X	X		21
Interstitial cell, adenoma					X								X					X							X	16
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma	X																									1
Subcutaneous tissue, skin, site of application, fibrosarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma																										1
Skeletal muscle								+																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule adenoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X					X	X			X		X		X								13
Lymphoma malignant	X																									1
Mesothelioma malignant															X							X				3

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	12/50 (24%)	6/50 (12%)	6/49 (12%)
Adjusted rate[b]	33.9%	17.3%	16.2%
Terminal rate[c]	2/8 (25%)	3/10 (30%)	4/14 (29%)
First incidence (days)	618	580	661
Poly-3 test[d]	P=0.044N	P=0.085N	P=0.063N
Adrenal Medulla: Benign or Complex Pheochromocytoma			
Overall rate	12/50 (24%)	6/50 (12%)	7/49 (14%)
Adjusted rate	33.9%	17.3%	18.7%
Terminal rate	2/8 (25%)	3/10 (30%)	4/14 (29%)
First incidence (days)	618	580	647
Poly-3 test	P=0.080N	P=0.085N	P=0.106N
Kidney (Renal Tubule): Adenoma			
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate	8.9%	11.6%	2.7%
Terminal rate	0/8 (0%)	1/10 (10%)	1/14 (7%)
First incidence (days)	654	611	728 (T)
Poly-3 test	P=0.208N	P=0.511	P=0.269N
Kidney (Renal Tubule): Adenoma or Carcinoma			
Overall rate	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted rate	11.8%	11.6%	2.7%
Terminal rate	0/8 (0%)	1/10 (10%)	1/14 (7%)
First incidence (days)	654	611	728 (T)
Poly-3 test	P=0.113N	P=0.638N	P=0.148N
Mammary Gland: Fibroadenoma			
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	8.9%	0.0%	2.7%
Terminal rate	2/8 (25%)	0/10 (0%)	0/14 (0%)
First incidence (days)	618	—[e]	723
Poly-3 test	P=0.165N	P=0.117N	P=0.268N
Mammary Gland: Fibroadenoma or Carcinoma			
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted rate	11.9%	0.0%	2.7%
Terminal rate	3/8 (38%)	0/10 (0%)	0/14 (0%)
First incidence (days)	618	—	723
Poly-3 test	P=0.072N	P=0.058N	P=0.146N
Pancreatic Islets: Adenoma			
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	3.0%	0.0%	8.0%
Terminal rate	0/8 (0%)	0/10 (0%)	1/14 (7%)
First incidence (days)	614	—	647
Poly-3 test	P=0.192	P=0.501N	P=0.344
Pancreatic Islets: Adenoma or Carcinoma			
Overall rate	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rate	8.9%	3.0%	10.7%
Terminal rate	1/8 (13%)	0/10 (0%)	2/14 (14%)
First incidence (days)	614	674	647
Poly-3 test	P=0.453	P=0.303N	P=0.560

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

	Vehicle Control	50 mg/kg	100 mg/kg
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	38/50 (76%)	38/50 (76%)	40/49 (82%)
Adjusted rate	83.6%	82.8%	86.7%
Terminal rate	6/8 (75%)	8/10 (80%)	12/14 (86%)
First incidence (days)	440	224	482
Poly-3 test	P=0.385	P=0.579N	P=0.447
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	5.9%	8.8%	5.3%
Terminal rate	1/8 (13%)	1/10 (10%)	0/14 (0%)
First incidence (days)	603	659	674
Poly-3 test	P=0.544N	P=0.504	P=0.656N
Testes: Adenoma			
Overall rate	24/50 (48%)	30/50 (60%)	37/50 (74%)
Adjusted rate	62.8%	72.6%	83.0%
Terminal rate	8/8 (100%)	9/10 (90%)	13/14 (93%)
First incidence (days)	440	440	526
Poly-3 test	P=0.011	P=0.212	P=0.015
Thyroid Gland (C-cell): Adenoma			
Overall rate	2/50 (4%)	5/50 (10%)	7/50 (14%)
Adjusted rate	5.9%	14.1%	18.6%
Terminal rate	0/8 (0%)	0/10 (0%)	3/14 (21%)
First incidence (days)	638	554	638
Poly-3 test	P=0.081	P=0.232	P=0.103
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	3/50 (6%)	6/50 (12%)	8/50 (16%)
Adjusted rate	8.9%	17.0%	21.1%
Terminal rate	1/8 (13%)	1/10 (10%)	3/14 (21%)
First incidence (days)	638	554	638
Poly-3 test	P=0.108	P=0.261	P=0.133
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	0.0%	11.6%	2.7%
Terminal rate	0/8 (0%)	1/10 (10%)	1/14 (7%)
First incidence (days)	—	580	728 (T)
Poly-3 test	P=0.464	P=0.063	P=0.522
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	0/50 (0%)	6/50 (12%)	2/50 (4%)
Adjusted rate	0.0%	17.2%	5.4%
Terminal rate	0/8 (0%)	2/10 (20%)	2/14 (14%)
First incidence (days)	—	580	728 (T)
Poly-3 test	P=0.324	P=0.016	P=0.262
All Organs: Mononuclear Cell Leukemia			
Overall rate	14/50 (28%)	13/50 (26%)	13/50 (26%)
Adjusted rate	37.7%	35.5%	32.6%
Terminal rate	5/8 (63%)	5/10 (50%)	3/14 (21%)
First incidence (days)	293	483	580
Poly-3 test	P=0.359N	P=0.519N	P=0.407N

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

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Malignant Mesothelioma			
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	6.0%	2.9%	8.0%
Terminal rate	1/8 (13%)	0/10 (0%)	2/14 (14%)
First incidence (days)	623	603	628
Poly-3 test	P=0.439	P=0.496N	P=0.550
All Organs: Benign Neoplasms			
Overall rate	47/50 (94%)	47/50 (94%)	49/50 (98%)
Adjusted rate	98.1%	97.4%	98.6%
Terminal rate	8/8 (100%)	10/10 (100%)	14/14 (100%)
First incidence (days)	440	224	482
Poly-3 test	P=0.600	P=0.738N	P=0.794
All Organs: Malignant Neoplasms			
Overall rate	21/50 (42%)	18/50 (36%)	22/50 (44%)
Adjusted rate	53.1%	47.7%	52.0%
Terminal rate	6/8 (75%)	7/10 (70%)	5/14 (36%)
First incidence (days)	293	483	526
Poly-3 test	P=0.514N	P=0.396N	P=0.551N
All Organs: Benign or Malignant Neoplasms			
Overall rate	49/50 (98%)	48/50 (96%)	50/50 (100%)
Adjusted rate	99.5%	98.8%	100.0%
Terminal rate	8/8 (100%)	10/10 (100%)	14/14 (100%)
First incidence (days)	293	224	482
Poly-3 test	P=0.694	P=0.894N	P=0.997

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary 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 Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	26	30	24
Natural deaths	16	10	12
Survivors			
Terminal sacrifice	8	10	14
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(49)	(48)	(49)
Mineralization		3 (6%)	2 (4%)
Parasite metazoan	3 (6%)	1 (2%)	2 (4%)
Intestine large, rectum	(48)	(49)	(48)
Mineralization		1 (2%)	1 (2%)
Parasite metazoan	2 (4%)		2 (4%)
Intestine large, cecum	(38)	(41)	(40)
Mineralization			1 (3%)
Intestine small, duodenum	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	
Mineralization		2 (4%)	2 (4%)
Ulcer			2 (4%)
Intestine small, jejunum	(42)	(45)	(43)
Inflammation, chronic active	1 (2%)	1 (2%)	
Mineralization		1 (2%)	
Ulcer		1 (2%)	
Intestine small, ileum	(41)	(45)	(45)
Parasite metazoan	1 (2%)		
Ulcer		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	1 (2%)
Basophilic focus	7 (14%)	11 (22%)	7 (14%)
Clear cell focus		2 (4%)	1 (2%)
Congestion	1 (2%)		
Degeneration	2 (4%)		
Eosinophilic focus		1 (2%)	
Hepatodiaphragmatic nodule	4 (8%)	7 (14%)	5 (10%)
Inflammation, chronic active	2 (4%)	4 (8%)	2 (4%)
Mixed cell focus	3 (6%)	3 (6%)	5 (10%)
Necrosis	2 (4%)		2 (4%)
Vacuolization cytoplasmic	10 (20%)	12 (24%)	15 (30%)
Bile duct, hyperplasia	3 (6%)	4 (8%)	2 (4%)
Mesentery	(5)	(7)	(3)
Mineralization	1 (20%)		
Fat, inflammation, chronic active	4 (80%)	5 (71%)	2 (67%)
Fat, mineralization		2 (29%)	
Fat, necrosis		1 (14%)	1 (33%)
Pancreas	(50)	(50)	(50)
Acinus, atrophy	3 (6%)	6 (12%)	3 (6%)
Acinus, hyperplasia		1 (2%)	
Duct, hyperplasia	1 (2%)		

[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 Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Stomach, forestomach	(50)	(50)	(50)
Edema	5 (10%)	6 (12%)	3 (6%)
Hyperkeratosis	14 (28%)	26 (52%)	11 (22%)
Hyperplasia, basal cell	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic active	12 (24%)	23 (46%)	11 (22%)
Inflammation, suppurative	3 (6%)	3 (6%)	1 (2%)
Mineralization	2 (4%)	1 (2%)	3 (6%)
Necrosis			2 (4%)
Perforation	4 (8%)	10 (20%)	1 (2%)
Ulcer	10 (20%)	14 (28%)	7 (14%)
Epithelium, hyperplasia	14 (28%)	25 (50%)	13 (26%)
Stomach, glandular	(50)	(49)	(50)
Erosion		1 (2%)	
Inflammation, chronic active	1 (2%)		
Mineralization	13 (26%)	6 (12%)	8 (16%)
Necrosis		1 (2%)	
Perforation		1 (2%)	
Ulcer	2 (4%)	1 (2%)	
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Mineralization	12 (24%)	5 (10%)	7 (14%)
Heart	(50)	(49)	(50)
Inflammation, chronic active	35 (70%)	38 (78%)	33 (66%)
Mineralization	7 (14%)	4 (8%)	7 (14%)
Thrombosis	1 (2%)	4 (8%)	1 (2%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Angiectasis	1 (2%)	2 (4%)	2 (4%)
Degeneration		1 (2%)	
Hemorrhage			1 (2%)
Hyperplasia	4 (8%)		1 (2%)
Vacuolization cytoplasmic	11 (22%)	23 (46%)	13 (26%)
Adrenal medulla	(50)	(50)	(49)
Hyperplasia	2 (4%)	3 (6%)	5 (10%)
Mineralization		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia		1 (2%)	
Parathyroid gland	(45)	(47)	(50)
Hyperplasia	17 (38%)	18 (38%)	12 (24%)
Pituitary gland	(50)	(50)	(49)
Cyst	1 (2%)	2 (4%)	2 (4%)
Fibrosis	1 (2%)		
Hemorrhage	2 (4%)		
Hyperplasia		2 (4%)	1 (2%)
Mineralization	1 (2%)	2 (4%)	1 (2%)
Pars distalis, angiectasis	2 (4%)		
Pars distalis, hyperplasia	2 (4%)	1 (2%)	1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System (continued)			
Thyroid gland	(50)	(50)	(50)
Atrophy	1 (2%)		
Ultimobranchial cyst	1 (2%)	1 (2%)	
C-cell, hyperplasia	1 (2%)		1 (2%)
Follicle, cyst		3 (6%)	1 (2%)
General Body System			
None			
Genital System			
Preputial gland	(50)	(50)	(50)
Cyst	8 (16%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)		
Inflammation	1 (2%)		
Inflammation, chronic active	32 (64%)	35 (70%)	38 (76%)
Mineralization	1 (2%)		1 (2%)
Prostate	(50)	(50)	(50)
Cyst	1 (2%)		1 (2%)
Hyperplasia	1 (2%)		
Inflammation, chronic active	10 (20%)	10 (20%)	7 (14%)
Inflammation, suppurative	1 (2%)	3 (6%)	
Mineralization		1 (2%)	
Seminal vesicle	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		2 (4%)
Mineralization		2 (4%)	
Testes	(50)	(50)	(50)
Cyst			1 (2%)
Degeneration	16 (32%)	14 (28%)	11 (22%)
Mineralization	4 (8%)	6 (12%)	5 (10%)
Necrosis	1 (2%)		
Interstitial cell, hyperplasia	28 (56%)	23 (46%)	20 (40%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Hyperplasia		1 (2%)	
Myelofibrosis	2 (4%)		
Lymph node	(2)		
Ectasia	1 (50%)		
Lymph node, mandibular	(49)	(49)	(49)
Ectasia	1 (2%)		
Hyperplasia		1 (2%)	
Lymph node, mesenteric	(49)	(48)	(50)
Congestion	1 (2%)		
Ectasia	2 (4%)	5 (10%)	5 (10%)
Hemorrhage		1 (2%)	
Hyperplasia		1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System (continued)			
Spleen	(50)	(50)	(50)
Congestion			1 (2%)
Depletion cellular		1 (2%)	
Fibrosis	6 (12%)	6 (12%)	5 (10%)
Hematopoietic cell proliferation	2 (4%)	6 (12%)	3 (6%)
Necrosis		1 (2%)	1 (2%)
Capsule, hyperplasia			1 (2%)
Thymus	(45)	(42)	(44)
Atrophy	1 (2%)		2 (5%)
Integumentary System			
Mammary gland	(49)	(49)	(49)
Dilatation	9 (18%)	16 (33%)	12 (24%)
Galactocele	6 (12%)	8 (16%)	10 (20%)
Hyperplasia	1 (2%)		
Mineralization	2 (4%)		
Pigmentation, hemosiderin	1 (2%)		
Skin	(50)	(50)	(50)
Epidermis, cyst		1 (2%)	
Sebaceous gland, skin, site of application, hyperplasia	1 (2%)	45 (90%)	45 (90%)
Skin, site of application, fibrosis			1 (2%)
Skin, site of application, hyperkeratosis		44 (88%)	40 (80%)
Skin, site of application, hyperplasia		49 (98%)	47 (94%)
Skin, site of application, inflammation, chronic active		48 (96%)	41 (82%)
Skin, site of application, mineralization			1 (2%)
Skin, site of application, parakeratosis		10 (20%)	11 (22%)
Skin, site of application, ulcer		7 (14%)	6 (12%)
Musculoskeletal System			
Bone	(50)	(49)	(50)
Fibrous osteodystrophy	9 (18%)	11 (22%)	6 (12%)
Skeletal muscle			(1)
Inflammation, chronic active			1 (100%)
Nervous System			
Brain	(50)	(50)	(50)
Hemorrhage			1 (2%)
Respiratory System			
Lung	(50)	(50)	(50)
Fibrosis			2 (4%)
Hemorrhage		1 (2%)	
Inflammation, chronic active	5 (10%)		4 (8%)
Inflammation, granulomatous		1 (2%)	
Mineralization	5 (10%)	3 (6%)	3 (6%)
Alveolar epithelium, hyperplasia		1 (2%)	1 (2%)
Mediastinum, fibrosis	1 (2%)		
Serosa, fibrosis		1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg
Respiratory System (continued)			
Nose	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	2 (4%)
Inflammation, suppurative	4 (8%)		3 (6%)
Trachea	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)		
Special Senses System			
Eye	(2)		(1)
Degeneration	1 (50%)		
Cornea, edema	1 (50%)		
Lens, mineralization	1 (50%)		1 (100%)
Retina, degeneration			1 (100%)
Harderian gland		(1)	
Hyperplasia		1 (100%)	
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)	
Casts		1 (2%)	
Cyst	5 (10%)	12 (24%)	4 (8%)
Inflammation, chronic active	1 (2%)		
Inflammation, suppurative		1 (2%)	
Mineralization	10 (20%)	5 (10%)	7 (14%)
Necrosis	1 (2%)		
Nephropathy	40 (80%)	42 (84%)	40 (80%)
Pigmentation, hemosiderin	5 (10%)	5 (10%)	8 (16%)
Renal tubule, degeneration	2 (4%)	1 (2%)	
Renal tubule, hyperplasia	1 (2%)		1 (2%)
Renal tubule, hyperplasia, oncocytic		1 (2%)	
Renal tubule, necrosis	1 (2%)		
Renal tubule, regeneration		1 (2%)	1 (2%)
Urinary bladder	(49)	(50)	(50)
Calculus, microscopic observation only		1 (2%)	
Fibrosis	1 (2%)		
Hemorrhage	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		1 (2%)
Ulcer		1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)		

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	11	9	5
Natural deaths	24	23	31
Survivors			
Terminal sacrifice	15	18	14
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(49)	(50)	(50)
Lipoma		1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)
Carcinoma	1 (2%)		
Liver	(50)	(50)	(50)
Hepatocellular adenoma	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Pancreas	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)
Schwannoma malignant	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Tongue			(1)
Squamous cell papilloma			1 (100%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)		1 (2%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	26 (52%)	19 (38%)	17 (34%)
Pars distalis, adenoma, multiple	3 (6%)	1 (2%)	2 (4%)
Thyroid gland	(50)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)		
C-cell, adenoma	3 (6%)	4 (8%)	2 (4%)
Follicular cell, adenoma		1 (2%)	
General Body System			
Tissue NOS		(1)	
Sarcoma		1 (100%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System			
Clitoral gland	(49)	(47)	(50)
Adenoma	9 (18%)	3 (6%)	4 (8%)
Carcinoma		1 (2%)	1 (2%)
Schwannoma malignant		1 (2%)	
Bilateral, adenoma	1 (2%)		
Ovary	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Sarcoma	1 (2%)		
Uterus	(50)	(50)	(50)
Adenoma	1 (2%)		
Deciduoma benign			1 (2%)
Polyp stromal	1 (2%)	2 (4%)	2 (4%)
Vagina	(1)		(1)
Polyp			1 (100%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Lymph node	(2)	(2)	(1)
Lymph node, mandibular	(49)	(49)	(49)
Histiocytic sarcoma	1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Spleen	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Thymus	(47)	(46)	(50)
Histiocytic sarcoma	1 (2%)		
Integumentary System			
Mammary gland	(49)	(49)	(50)
Adenoma		1 (2%)	
Carcinoma	1 (2%)		3 (6%)
Fibroadenoma	9 (18%)	10 (20%)	6 (12%)
Mixed tumor malignant		1 (2%)	
Skin	(50)	(50)	(50)
Melanoma malignant	1 (2%)		
Subcutaneous tissue, fibroma		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
Nervous System			
Brain	(50)	(50)	(50)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Adenoma	1 (2%)		
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)
Chordoma, metastatic, uncertain primary site		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Squamous cell carcinoma	1 (2%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
Renal tubule, adenoma, multiple			1 (2%)
Urinary bladder	(50)	(49)	(49)
Transitional epithelium, carcinoma		1 (2%)	
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Leukemia mononuclear	5 (10%)	9 (18%)	8 (16%)
Lymphoma malignant		1 (2%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]	40	34	32
Total primary neoplasms	70	61	51
Total animals with benign neoplasms	38	28	26
Total benign neoplasms	58	45	39
Total animals with malignant neoplasms	12	15	12
Total malignant neoplasms	12	16	12
Total animals with metastatic neoplasms		1	
Total metastatic neoplasms		1	
Total animals with malignant neoplasms of uncertain primary site		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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: Vehicle Control

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

+: 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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	6 6 8	6 7 6	6 7 9	6 9 2	6 9 4	6 9 5	6 9 6	6 9 8	7 0 6	7 1 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	1 5 6	1 7 7	1 9 3	1 6 9	1 9 2	1 9 0	1 6 3	1 5 3	1 8 3	2 0 0	1 5 2	1 6 1	1 6 2	1 6 4	1 6 6	1 6 8	1 7 1	1 7 3	1 7 4	1 7 5	1 7 6	1 8 6	1 8 7	1 8 8	1 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, cecum	A	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	29
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine small, ileum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Histiocytic sarcoma																										1
Mesentery																			+							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X															X					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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			26
Pars distalis, adenoma, multiple								X																X		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma											X															1
C-cell, adenoma			X	X															X							3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X		X													X		X		X			X	9
Bilateral, adenoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Sarcoma																										1
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Polyp stromal																										1
Vagina																									+	1

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

Number of Days on Study	2 9 6	4 2 3	4 2 9	4 3 7	4 4 7	4 6 2	4 6 2	4 9 7	5 1 3	5 2 4	5 2 9	5 4 5	5 6 0	5 7 1	5 7 9	5 8 6	6 0 2	6 1 0	6 1 4	6 3 5	6 3 5	6 3 5	6 4 1	6 4 1	6 5 3
Carcass ID Number	1 9 4	1 5 4	1 9 5	1 5 9	1 7 2	1 6 7	1 8 0	1 6 5	1 7 0	1 5 5	1 7 8	1 8 2	1 7 9	1 9 6	1 6 0	1 5 8	1 9 1	1 8 5	1 9 7	1 8 1	1 8 4	1 9 9	1 5 1	1 8 9	1 5 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Lymph node																				+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma								X										X				X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Histiocytic sarcoma															X										
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																								+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Leukemia mononuclear																				X					

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

Number of Days on Study	668	676	679	692	694	695	696	698	706	718	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	15696	15767	15793	15969	15992	16090	16093	16053	16083	16200	16052	16061	16062	16064	16066	16068	16071	16073	16074	16075	16076	16086	16087	16088	16098	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node			+																							2
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Carcinoma																		X								1
Fibroadenoma										X	X			X							X			X		9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Histiocytic sarcoma																										1
Squamous cell carcinoma														X												1
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+				+														3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear						X			X										X					X		5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	244	270	284	288	371	397	429	508	524	528	541	511	544	545	546	547	567	579	622	623	630	635	658	662	667
Carcass ID Number	231	232	248	201	213	202	247	229	249	209	207	225	240	236	239	208	226	220	205	250	212	224	244	218	228
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+
Intestine large, cecum	A	A	+	A	A	A	A	A	A	A	+	+	A	A	A	+	A	+	A	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	A	A	A	+	A	+	+	A	A	A	+	+	+	+	A	+	+	+	A	+
Intestine small, ileum	+	+	+	+	+	A	+	+	A	A	+	+	A	+	A	+	A	+	A	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+						+									
Oral mucosa																					+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X			X	X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X												X
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Sarcoma																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Adenoma																									
Carcinoma																									
Schwannoma malignant																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																							+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	6 7 4	6 8 5	6 8 5	6 9 3	7 0 2	7 1 9	7 2 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 1 3	2 1 1	2 4 1	2 1 9	2 3 3	2 3 5	2 0 4	2 0 3	2 0 6	2 1 0	2 1 4	2 1 5	2 1 6	2 1 7	2 2 0	2 2 1	2 2 7	2 3 0	2 3 4	2 3 7	2 3 8	2 4 2	2 4 3	2 4 5	2 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma													X													1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																			+							3
Oral mucosa																										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
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X	X	X	X	X				X	X	X	X	X						X	X	X	19
Pars distalis, adenoma, multiple																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X													X	4
Follicular cell, adenoma				X																						1
General Body System																										
Tissue NOS		+																								1
Sarcoma		X																								1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X				X												X							3
Carcinoma																									X	1
Schwannoma malignant														X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal														X				X								2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	244	270	284	289	371	397	429	508	524	528	541	511	544	545	546	547	567	579	622	623	630	635	658	662	667
Carcass ID Number	231	232	248	201	213	202	247	229	249	209	207	225	240	236	239	208	226	222	205	250	212	244	244	218	228
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																									
Fibroadenoma																		X		X		X			
Mixed tumor malignant												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Chordoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Transitional epithelium, carcinoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X			X				X	X
Lymphoma malignant																							X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 50 mg/kg

Number of Days on Study	674	685	685	693	702	719	722	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	
Carcass ID Number	21313	21131	24141	21319	23333	23535	20404	20003	20006	21010	21414	21515	21616	21717	22020	22121	22427	23030	23434	23737	23838	24242	24343	24545	24646	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											1
Fibroadenoma	X		X		X			X										X				X		X		10
Mixed tumor malignant																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																X										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															1
Chordoma, metastatic, uncertain primary site		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+											+													3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma							X																			1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X					X			X									X				9
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	1 6 9	1 7 0	3 0 2	3 0 5	3 1 3	3 3 1	3 5 5	3 5 6	3 9 4	4 1 9	4 3 4	4 5 9	4 6 3	5 0 1	5 1 8	5 1 8	5 1 9	5 2 6	5 3 5	5 3 5	5 4 9	5 6 0	5 6 1	5 6 3	5 6 8
Carcass ID Number	2 8 9	2 7 1	2 6 1	2 8 5	2 9 4	2 6 6	2 5 3	2 7 5	2 8 8	2 9 1	2 9 3	2 7 6	2 5 4	2 9 6	2 5 9	2 9 7	2 8 3	2 7 8	2 6 5	2 7 2	2 5 5	2 6 8	3 0 0	2 8 1	2 5 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	A	+	A	A	A	A	A	A	A	+	A	A	A	A	+	A	A	A	+	A	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	A	+	A	+	+	A	+	A	+	+	A	A	+	+	A	+	+	+	+	+
Intestine small, ileum	+	+	A	+	A	+	+	A	A	+	+	A	+	A	A	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X		X					X		X		
Pars distalis, adenoma, multiple																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign																									
Polyp stromal										X															
Vagina																									
Polyp																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	5 7 4	5 9 5	6 2 1	6 3 7	6 4 4	6 7 3	6 8 1	6 9 2	6 9 5	7 0 9	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 6 4	2 5 2	2 8 6	2 9 9	2 7 0	2 8 2	2 7 4	2 5 6	2 8 4	2 5 8	2 7 3	2 5 1	2 6 0	2 6 2	2 6 3	2 6 7	2 6 9	2 7 7	2 7 9	2 8 0	2 8 7	2 9 0	2 9 2	2 9 5	2 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	28
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																	+									1
Squamous cell papilloma																	X									1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X		X		X	X		X			X	X	X				X	X			X		17
Pars distalis, adenoma, multiple													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																							X			2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X	X									X						4
Carcinoma																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma benign																	X									1
Polyp stromal																			X							2
Vagina											+															1
Polyp											X															1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	1 1 3 3 3 3 3 3 3 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5
	6 7 0 0 1 3 5 5 9 1 3 5 6 0 1 1 1 2 3 3 4 6 6 6 6
	9 0 2 5 3 1 5 6 4 9 4 9 3 1 8 8 9 6 5 5 9 0 1 3 8
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 2 2
	8 7 6 8 9 6 5 7 8 9 9 7 5 9 5 9 8 7 6 7 5 6 0 8 5
	9 1 1 5 4 6 3 5 8 1 3 6 4 6 9 7 3 8 5 2 5 8 0 1 7
Integumentary System	
Mammary gland	+ +
Carcinoma	
Fibroadenoma	
Skin	+ +
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ +
Urinary System	
Kidney	+ +
Renal tubule, adenoma, multiple	
Urinary bladder	+ M + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	5 7 4	5 9 5	6 2 1	6 3 7	6 4 4	6 7 3	6 8 1	6 9 2	6 9 5	7 0 9	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 6 4	2 5 2	2 8 6	2 9 9	2 7 0	2 8 2	2 7 4	2 5 6	2 8 4	2 5 8	2 7 3	2 5 1	2 6 0	2 6 2	2 6 3	2 6 7	2 6 9	2 7 7	2 7 9	2 8 0	2 8 7	2 9 0	2 9 2	2 9 5	2 9 8	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X														X	X			3
Fibroadenoma				X							X			X	X								X	X		6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye															+	+			+		+					6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma, multiple																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X	X			X							X	X								8

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

	Vehicle Control	50 mg/kg	100 mg/kg
Clitoral Gland: Adenoma			
Overall rate[a]	10/49 (20%)	3/47 (6%)	4/50 (8%)
Adjusted rate[b]	27.6%	9.4%	13.6%
Terminal rate[c]	4/15 (27%)	1/17 (6%)	1/14 (7%)
First incidence (days)	524	685	526
Poly-3 test[d]	P=0.066N	P=0.050N	P=0.138N
Clitoral Gland: Adenoma or Carcinoma			
Overall rate	10/49 (20%)	4/47 (9%)	5/50 (10%)
Adjusted rate	27.6%	12.5%	17.0%
Terminal rate	4/15 (27%)	2/17 (12%)	2/14 (14%)
First incidence (days)	524	685	526
Poly-3 test	P=0.143N	P=0.102N	P=0.232N
Mammary Gland: Fibroadenoma			
Overall rate	9/50 (18%)	10/50 (20%)	6/50 (12%)
Adjusted rate	24.7%	27.8%	20.6%
Terminal rate	4/15 (27%)	4/18 (22%)	4/14 (29%)
First incidence (days)	497	579	637
Poly-3 test	P=0.444N	P=0.487	P=0.461N
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	9/50 (18%)	11/50 (22%)	6/50 (12%)
Adjusted rate	24.7%	30.6%	20.6%
Terminal rate	4/15 (27%)	5/18 (28%)	4/14 (29%)
First incidence (days)	497	579	637
Poly-3 test	P=0.462N	P=0.381	P=0.461N
Mammary Gland: Carcinoma			
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.9%	0.0%	10.4%
Terminal rate	1/15 (7%)	0/18 (0%)	2/14 (14%)
First incidence (days)	728 (T)	—[e]	692
Poly-3 test	P=0.166	P=0.502N	P=0.241
Mammary Gland: Adenoma or Carcinoma			
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.9%	2.9%	10.4%
Terminal rate	1/15 (7%)	1/18 (6%)	2/14 (14%)
First incidence (days)	728 (T)	728 (T)	692
Poly-3 test	P=0.175	P=0.759	P=0.241
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	10/50 (20%)	11/50 (22%)	8/50 (16%)
Adjusted rate	27.5%	30.6%	27.3%
Terminal rate	5/15 (33%)	5/18 (28%)	5/14 (36%)
First incidence (days)	497	579	637
Poly-3 test	P=0.546	P=0.485	P=0.607N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	29/50 (58%)	20/50 (40%)	19/50 (38%)
Adjusted rate	70.7%	55.7%	56.6%
Terminal rate	10/15 (67%)	11/18 (61%)	7/14 (50%)
First incidence (days)	462	622	501
Poly-3 test	P=0.093N	P=0.109N	P=0.134N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland (C-cell): Adenoma			
Overall rate	4/50 (8%)	4/50 (8%)	2/50 (4%)
Adjusted rate	11.4%	11.4%	6.7%
Terminal rate	2/15 (13%)	2/18 (11%)	1/14 (7%)
First incidence (days)	679	544	355
Poly-3 test	P=0.361N	P=0.645N	P=0.415N
All Organs: Mononuclear Cell Leukemia			
Overall rate	5/50 (10%)	9/50 (18%)	8/50 (16%)
Adjusted rate	14.2%	25.0%	25.6%
Terminal rate	2/15 (13%)	3/18 (17%)	2/14 (14%)
First incidence (days)	635	547	169
Poly-3 test	P=0.153	P=0.194	P=0.191
All Organs: Benign Neoplasms			
Overall rate	38/50 (76%)	28/50 (56%)	26/50 (52%)
Adjusted rate	86.5%	74.5%	72.3%
Terminal rate	13/15 (87%)	15/18 (83%)	10/14 (71%)
First incidence (days)	462	544	355
Poly-3 test	P=0.045N	P=0.101N	P=0.067N
All Organs: Malignant Neoplasms			
Overall rate	12/50 (24%)	15/50 (30%)	12/50 (24%)
Adjusted rate	31.7%	40.7%	38.3%
Terminal rate	4/15 (27%)	6/18 (33%)	5/14 (36%)
First incidence (days)	429	541	169
Poly-3 test	P=0.309	P=0.280	P=0.374
All Organs: Benign or Malignant Neoplasms			
Overall rate	40/50 (80%)	34/50 (68%)	32/50 (64%)
Adjusted rate	88.5%	86.8%	85.4%
Terminal rate	13/15 (87%)	17/18 (94%)	13/14 (93%)
First incidence (days)	429	541	169
Poly-3 test	P=0.386N	P=0.548N	P=0.462N

(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, 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 B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	11	9	5
Natural deaths	24	23	31
Survivors			
Terminal sacrifice	15	18	14
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(49)	(50)	(50)
Foreign body	1 (2%)		
Perforation		1 (2%)	
Intestine large, colon	(47)	(50)	(48)
Parasite metazoan	2 (4%)	3 (6%)	4 (8%)
Intestine large, rectum	(38)	(47)	(46)
Parasite metazoan	1 (3%)	1 (2%)	2 (4%)
Intestine small, jejunum	(36)	(38)	(38)
Inflammation, chronic active		1 (3%)	
Necrosis		1 (3%)	
Liver	(50)	(50)	(50)
Angiectasis		1 (2%)	
Basophilic focus	18 (36%)	15 (30%)	11 (22%)
Clear cell focus		1 (2%)	
Eosinophilic focus		3 (6%)	
Hepatodiaphragmatic nodule	7 (14%)	14 (28%)	11 (22%)
Hyperplasia	1 (2%)		
Inflammation, chronic active	13 (26%)	7 (14%)	9 (18%)
Mixed cell focus	1 (2%)	2 (4%)	
Necrosis	1 (2%)		
Vacuolization cytoplasmic	3 (6%)	3 (6%)	2 (4%)
Bile duct, dilatation		1 (2%)	
Mesentery	(3)	(3)	
Fat, inflammation, chronic active	3 (100%)	3 (100%)	
Pancreas	(50)	(50)	(50)
Fibrosis			1 (2%)
Acinus, atrophy	3 (6%)	5 (10%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)	
Ulcer	1 (2%)	5 (10%)	2 (4%)
Epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)
Mineralization			1 (2%)
Necrosis		1 (2%)	
Ulcer	1 (2%)		

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Cardiovascular System			
Heart	(50)	(50)	(50)
Fibrosis		1 (2%)	
Inflammation, chronic active	18 (36%)	20 (40%)	14 (28%)
Thrombosis	1 (2%)	1 (2%)	
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule			2 (4%)
Angiectasis	25 (50%)	19 (38%)	26 (52%)
Degeneration	1 (2%)		1 (2%)
Fibrosis		1 (2%)	
Hematopoietic cell proliferation	1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	2 (4%)
Mineralization		1 (2%)	
Pigmentation, lipofuscin			1 (2%)
Vacuolization cytoplasmic	7 (14%)	7 (14%)	4 (8%)
Islets, pancreatic	(50)	(50)	(50)
Vacuolization cytoplasmic	1 (2%)		
Parathyroid gland	(42)	(43)	(42)
Hyperplasia			1 (2%)
Pituitary gland	(50)	(50)	(50)
Angiectasis	3 (6%)	2 (4%)	4 (8%)
Cyst	8 (16%)	6 (12%)	5 (10%)
Hemorrhage		1 (2%)	1 (2%)
Pars distalis, angiectasis	8 (16%)	2 (4%)	4 (8%)
Pars distalis, hyperplasia	4 (8%)	4 (8%)	9 (18%)
Thyroid gland	(50)	(50)	(50)
Atrophy	1 (2%)		
Ultimobranchial cyst	2 (4%)	1 (2%)	
C-cell, hyperplasia	1 (2%)	1 (2%)	
Follicle, cyst	1 (2%)	1 (2%)	
General Body System			
None			
Genital System			
Clitoral gland	(49)	(47)	(50)
Cyst	2 (4%)	2 (4%)	1 (2%)
Hyperplasia		1 (2%)	
Inflammation, chronic active	46 (94%)	44 (94%)	43 (86%)
Ovary	(50)	(50)	(50)
Atrophy			1 (2%)
Congestion		1 (2%)	
Cyst		3 (6%)	
Pigmentation, lipofuscin		1 (2%)	
Follicle, cyst		1 (2%)	
Periovarian tissue, cyst	3 (6%)	8 (16%)	3 (6%)
Oviduct	(1)		
Cyst	1 (100%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System (continued)			
Uterus	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Hydrometra		4 (8%)	2 (4%)
Vagina	(1)		(1)
Hypertrophy	1 (100%)		
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Myelofibrosis		1 (2%)	
Lymph node	(2)	(2)	(1)
Ectasia	1 (50%)		
Pigmentation, hemosiderin		1 (50%)	
Pigmentation, lipofuscin		1 (50%)	
Lymph node, mesenteric	(50)	(50)	(50)
Ectasia	1 (2%)	1 (2%)	
Necrosis		1 (2%)	
Spleen	(50)	(50)	(50)
Accessory spleen	1 (2%)	1 (2%)	
Fibrosis	3 (6%)		
Hematopoietic cell proliferation	1 (2%)		1 (2%)
Necrosis		1 (2%)	
Integumentary System			
Mammary gland	(49)	(49)	(50)
Dilatation	9 (18%)	11 (22%)	7 (14%)
Galactocele	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active		1 (2%)	
Skin	(50)	(50)	(50)
Sebaceous gland, skin, site of application, hyperplasia	2 (4%)	48 (96%)	49 (98%)
Skin, site of application, hyperkeratosis	1 (2%)	38 (76%)	31 (62%)
Skin, site of application, hyperplasia	3 (6%)	50 (100%)	50 (100%)
Skin, site of application, inflammation, chronic active	2 (4%)	44 (88%)	48 (96%)
Skin, site of application, parakeratosis	2 (4%)	27 (54%)	43 (86%)
Skin, site of application, ulcer	3 (6%)	20 (40%)	36 (72%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
Osteosclerosis	5 (10%)		1 (2%)
Nervous System			
None			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Congestion		2 (4%)	2 (4%)
Edema			1 (2%)
Inflammation, chronic active	5 (10%)	3 (6%)	4 (8%)
Mineralization			1 (2%)
Necrosis		1 (2%)	
Pigmentation, hemosiderin	1 (2%)		1 (2%)
Nose	(49)	(50)	(50)
Inflammation, suppurative	2 (4%)	2 (4%)	1 (2%)
Trachea	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	1 (2%)
Special Senses System			
Eye	(3)	(3)	(6)
Mineralization	1 (33%)	1 (33%)	1 (17%)
Retinal detachment		1 (33%)	
Lens, cataract			1 (17%)
Lens, mineralization		1 (33%)	3 (50%)
Retina, degeneration	2 (67%)	3 (100%)	4 (67%)
Urinary System			
Kidney	(50)	(50)	(50)
Casts protein	1 (2%)		
Cyst	1 (2%)		
Mineralization	35 (70%)	37 (74%)	37 (74%)
Nephropathy	9 (18%)	8 (16%)	5 (10%)
Pigmentation, hemosiderin	4 (8%)	3 (6%)	
Renal tubule, degeneration		1 (2%)	
Renal tubule, hyperplasia	2 (4%)	1 (2%)	
Renal tubule, regeneration	1 (2%)	2 (4%)	2 (4%)
Urinary bladder	(50)	(49)	(49)
Inflammation, chronic active		1 (2%)	2 (4%)
Mineralization		1 (2%)	

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

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

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	55	55	55
3-Month interim evaluation	5	5	5
Early deaths			
Moribund	3	8	11
Natural deaths	5	7	5
Survivors			
Terminal sacrifice	41	35	34
Missing	1		
Animals examined microscopically	54	55	55
Systems Examined at 3 Months with No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Intestine small, duodenum	(48)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Intestine small, jejunum	(49)	(50)	(50)
Carcinoma	2 (4%)		
Hepatocholangiocarcinoma, metastatic, liver		2 (4%)	
Intestine small, ileum	(49)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Liver	(49)	(50)	(50)
Fibrous histiocytoma	1 (2%)		
Hemangiosarcoma		2 (4%)	1 (2%)
Hemangiosarcoma, multiple	1 (2%)	2 (4%)	1 (2%)
Hepatoblastoma			1 (2%)
Hepatocellular carcinoma	5 (10%)	9 (18%)	12 (24%)
Hepatocellular carcinoma, multiple	4 (8%)		1 (2%)
Hepatocellular adenoma	13 (27%)	14 (28%)	14 (28%)
Hepatocellular adenoma, multiple	9 (18%)	8 (16%)	8 (16%)
Hepatocholangiocarcinoma		2 (4%)	1 (2%)
Histiocytic sarcoma		1 (2%)	
Mesentery	(4)	(4)	(3)
Fibrous histiocytoma, metastatic, liver	1 (25%)		

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Pancreas	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Salivary glands	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Stomach, forestomach	(49)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Squamous cell papilloma		2 (4%)	
Stomach, glandular	(49)	(50)	(50)
Adenoma		1 (2%)	
Cardiovascular System			
Blood vessel	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Heart	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)
Endocrine System			
Adrenal cortex	(49)	(50)	(50)
Adenoma	2 (4%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Adrenal medulla	(49)	(50)	(50)
Islets, pancreatic	(49)	(50)	(50)
Adenoma		2 (4%)	2 (4%)
Thyroid gland	(49)	(50)	(50)
Adenoma			1 (2%)
Follicular cell, adenoma	2 (4%)		1 (2%)
Follicular cell, carcinoma	1 (2%)		
General Body System			
None			
Genital System			
Epididymis	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Preputial gland	(48)	(50)	(50)
Hemangioma		1 (2%)	
Prostate	(49)	(50)	(50)
Seminal vesicle	(49)	(50)	(50)
Testes	(49)	(50)	(50)
Hemangioma			1 (2%)
Interstitial cell, adenoma		1 (2%)	1 (2%)

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hemangiosarcoma			2 (4%)
Hemangiosarcoma, metastatic, spleen		1 (2%)	
Lymph node	(3)	(4)	(1)
Lumbar, fibrous histiocytoma, metastatic, liver	1 (33%)		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (25%)	
Pancreatic, hepatocellular carcinoma, metastatic, liver	1 (33%)		
Renal, fibrous histiocytoma, metastatic, liver	1 (33%)		
Lymph node, mandibular	(48)	(46)	(47)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Lymph node, mesenteric	(47)	(48)	(48)
Spleen	(49)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma	3 (6%)	4 (8%)	2 (4%)
Hemangiosarcoma, multiple		1 (2%)	
Thymus	(45)	(36)	(39)
Hemangioma			1 (3%)
Integumentary System			
Skin	(49)	(50)	(50)
Fibrosarcoma			1 (2%)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (2%)	
Schwannoma benign		1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Musculoskeletal System			
Skeletal muscle		(1)	
Hepatocholangiocarcinoma, metastatic, liver		1 (100%)	
Nervous System			
None			
Respiratory System			
Lung	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	8 (16%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	6 (12%)	8 (16%)	9 (18%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)	2 (4%)	
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, spleen			1 (2%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)	5 (10%)
Hepatocholangiocarcinoma, metastatic, liver		2 (4%)	3 (6%)
Mediastinum, hemangioma			1 (2%)
Nose	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Special Senses System			
Harderian gland	(2)	(1)	(5)
Adenoma	2 (100%)	1 (100%)	4 (80%)
Urinary System			
Kidney	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)
Urinary bladder	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, liver	1 (2%)		
Leiomyosarcoma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
Lymphoma malignant	1 (2%)	6 (12%)	2 (4%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	42	43	44
Total primary neoplasms	61	77	74
Total animals with benign neoplasms	28	30	32
Total benign neoplasms	35	39	40
Total animals with malignant neoplasms	24	29	25
Total malignant neoplasms	26	38	34
Total animals with metastatic neoplasms	5	6	9
Total metastatic neoplasms	18	16	11

[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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	4 5 2	4 5 6	4 8 5	5 6 1	6 6 7	6 9 1	6 9 5	6 9 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 3 0	0 2 4	0 4 3	0 5 0	0 0 7	0 0 6	0 4 8	0 5 3	0 0 1	0 0 4	0 0 8	0 1 0	0 1 1	0 1 3	0 1 4	0 1 5	0 2 0	0 2 2	0 2 3	0 2 7	0 2 9	0 3 3	0 3 5	0 3 9
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma			X																					
Hemangiosarcoma, multiple																								
Hepatocellular carcinoma	X			X	X																			
Hepatocellular carcinoma, multiple						X		X										X						
Hepatocellular adenoma		X	X							X							X	X	X			X		
Hepatocellular adenoma, multiple									X				X			X					X			
Mesentery			+				+														+			
Fibrous histiocytoma, metastatic, liver			X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X				X										
Follicular cell, carcinoma												X												
General Body System																								
None																								

+: 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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	04 6	04 7	05 1	05 2	05 4	00 3	00 5	00 9	01 2	01 6	01 9	02 1	02 5	02 8	03 1	03 2	03 4	03 6	03 7	03 8	04 1	04 2	04 5	04 9	05 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma											X															2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Hemangiosarcoma, multiple																					X					1
Hepatocellular carcinoma															X		X									5
Hepatocellular carcinoma, multiple			X																							4
Hepatocellular adenoma					X	X	X		X				X					X								13
Hepatocellular adenoma, multiple								X								X	X		X				X			9
Mesentery																			+							4
Fibrous histiocytoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									X	2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										2
Follicular cell, carcinoma																										1
General Body System																										
None																										

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

Number of Days on Study	4 5 2	4 5 6	4 8 5	5 6 1	6 6 7	6 9 1	6 9 5	6 9 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 3 0	0 2 4	0 4 3	0 5 0	0 0 7	0 0 6	0 4 8	0 5 3	0 0 1	0 0 4	0 0 8	0 1 0	1 1 1	1 1 3	1 1 4	1 1 5	2 2 0	2 2 2	2 2 3	2 2 7	2 2 9	3 3 3	3 3 5	3 3 9
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Lymph node			+				+																	
Lumbar, fibrous histiocytoma, metastatic, liver			X																					
Pancreatic, hepatocellular carcinoma, metastatic, liver																								
Renal, fibrous histiocytoma, metastatic, liver			X																					
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X															X	X					X		
Alveolar/bronchiolar adenoma, multiple																					X			
Alveolar/bronchiolar carcinoma																X				X		X		
Alveolar/bronchiolar carcinoma, multiple												X												
Fibrous histiocytoma, metastatic, liver			X																					
Hepatocellular carcinoma, metastatic, liver						X		X										X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland											+													
Adenoma											X													

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

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	04 46	04 47	05 01	05 02	05 04	00 03	00 05	00 09	01 02	01 06	01 09	02 01	02 05	02 08	03 01	03 02	03 04	03 06	03 07	03 08	04 01	04 02	04 05	04 09	05 05	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Lymph node															+											3
Lumbar, fibrous histiocytoma, metastatic, liver																										1
Pancreatic, hepatocellular carcinoma, metastatic, liver															X											1
Renal, fibrous histiocytoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrous histiocytoma, metastatic, liver																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma	X								X																	3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	45
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																						X		X		6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma				X	X								X													6
Alveolar/bronchiolar carcinoma, multiple																										1
Fibrous histiocytoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland																		+								2
Adenoma																		X								2

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

Number of Days on Study	4 5 2	4 5 6	4 8 5	5 6 1	6 6 7	6 9 1	6 9 5	6 9 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 3 0	0 2 4	0 4 3	0 5 0	0 0 7	0 0 6	0 4 8	0 5 3	0 0 1	0 0 4	0 0 8	0 1 0	0 1 1	0 1 3	0 1 4	0 1 5	0 2 0	0 2 2	0 2 3	0 2 7	0 2 9	0 3 3	0 3 5	0 3 9
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver			X																					
Leiomyosarcoma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X																	

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

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	04 46	04 47	05 01	05 02	05 04	00 03	00 05	00 09	01 02	01 06	01 09	02 01	02 05	02 08	03 01	03 02	03 04	03 06	03 07	03 08	04 01	04 02	04 05	04 09	05 05	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver																										1
Leiomyosarcoma											X															1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	1 7 6	4 2 5	5 4 7	5 6 7	6 2 1	6 2 4	6 2 8	6 2 8	6 6 0	6 8 6	6 9 7	7 0 8	7 0 9	7 1 2	7 2 0	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 0 5	1 0 8	0 7 1	1 0 6	0 0 0	0 9 8	0 8 6	1 0 0	0 9 2	1 0 9	1 0 4	0 8 7	1 1 0	0 1 8	0 8 1	0 6 4	0 6 5	0 6 8	0 6 9	0 7 4	0 7 5	0 7 6	0 7 7	0 7 8	0 7 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver										X	X														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Hemangiosarcoma, multiple																						X			
Hepatocellular carcinoma			X			X						X	X	X											
Hepatocellular adenoma									X			X	X									X			
Hepatocellular adenoma, multiple																X							X		
Hepatocholangiocarcinoma										X	X														
Histiocytic sarcoma				X																					
Mesentery															+							+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	08383	08585	08991	09494	09905	10103	10107	10506	10557	10558	10559	10560	10661	10663	10666	10667	10672	10773	10782	10788	10889	10897	10997	10999	11011	11012	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																					2
Hemangiosarcoma, multiple								X																			2
Hepatocellular carcinoma						X	X					X										X					9
Hepatocellular adenoma	X				X	X			X				X		X			X			X	X	X				14
Hepatocellular adenoma, multiple		X	X	X						X							X		X								8
Hepatocholangiocarcinoma																											2
Histiocytic sarcoma																											1
Mesentery																	+									+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma	X																										1
Squamous cell papilloma																							X				2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen				X																							1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X			2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+		42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
None																											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	1 7 6	4 2 5	5 4 7	5 6 7	6 2 1	6 2 4	6 2 8	6 2 8	6 6 0	6 8 6	6 9 7	7 0 8	7 0 9	7 1 2	7 2 0	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 0 5	1 0 8	0 7 1	1 0 6	0 0 9	0 9 8	0 8 6	1 0 0	0 9 0	1 0 9	1 0 4	0 8 7	1 1 0	0 0 8	0 8 1	0 6 4	0 6 5	0 6 8	0 6 9	0 7 4	0 7 5	0 7 6	0 7 7	0 7 8	0 7 9
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung														X											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma												X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Lymph node					+			+						+	+										
Mediastinal, alveolar/bronchiolar																									
Carcinoma, metastatic, lung														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X					X					X				
Hemangiosarcoma, multiple																									
Thymus	+	+	+	M	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Schwannoma benign			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Hepatocholangiocarcinoma, metastatic, liver											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X										X	X		X			X				
Alveolar/bronchiolar carcinoma			X																	X					
Alveolar/bronchiolar carcinoma, multiple							X							X											
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver										X	X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	08 3	08 5	09 1	09 4	09 5	10 3	10 7	05 6	05 7	05 8	05 9	06 0	06 1	06 3	06 6	06 7	07 2	07 3	08 2	08 8	08 9	09 7	09 9	10 1	10 2	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen				X																						1
Lymph node																										4
Mediastinal, alveolar/bronchiolar																										
Carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		4
Hemangiosarcoma, multiple				X																						1
Thymus	+	+	+	+	+	+	+	+	+	+	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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen				X																						1
Schwannoma benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X		X			X						8
Alveolar/bronchiolar carcinoma	X						X				X	X		X					X							8
Alveolar/bronchiolar carcinoma, multiple																										2
Hepatocellular carcinoma, metastatic, liver						X	X																			2
Hepatocholangiocarcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+																									1
Adenoma	X																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	08383	08585	09191	09494	09595	10003	10107	10256	10557	10558	10559	10560	10601	10603	10606	10607	10672	10773	10822	10888	10889	10897	10997	11001	11002		Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Lymphoma malignant			X																								6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 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	730	730	730	730	730	
Carcass ID Number	14 45	14 46	14 48	15 01	15 02	15 04	15 55	15 58	11 11	11 12	11 13	11 16	11 17	11 18	12 01	12 23	12 25	12 28	13 30	14 44	14 49	15 00	15 03	15 56	16 65	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hepatoblastoma																										1
Hepatocellular carcinoma		X		X				X					X				X					X			X	12
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X				X						X					X	X						X	X		14
Hepatocellular adenoma, multiple				X								X							X	X	X	X				8
Hepatocholangiocarcinoma																										1
Mesentery		+															+									3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																	X	2
Parathyroid gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Interstitial cell, adenoma														X												1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 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	730	730	730	730	730	730	
Carcass ID Number	14 5	14 6	14 8	15 1	15 2	15 4	15 5	15 8	11 1	11 2	11 3	11 6	11 7	11 8	12 1	12 3	12 5	12 8	13 0	14 4	14 9	15 0	15 3	15 6	16 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	2
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma									X																	2
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	39
Hemangioma																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X					X						X									X		4
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma	X	X					X						X	X		X								X	X	9
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma, metastatic, liver		X											X				X					X				5
Hepatocholangiocarcinoma, metastatic, liver																										3
Mediastinum, hemangioma																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																	+									5
Adenoma																	X									4
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant									X																	2

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

	Vehicle Control	15 mg/kg	30 mg/kg
Harderian Gland: Adenoma			
Overall rate[a]	2/49 (4%)	1/50 (2%)	4/50 (8%)
Adjusted rate[b]	4.4%	2.2%	9.3%
Terminal rate[c]	2/41 (5%)	1/35 (3%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	638
Poly-3 test[d]	P=0.229	P=0.506N	P=0.311
Liver: Hemangiosarcoma			
Overall rate	1/49 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.2%	8.9%	4.6%
Terminal rate	1/41 (2%)	4/35 (11%)	1/34 (3%)
First incidence (days)	729 (T)	729 (T)	468
Poly-3 test	P=0.377	P=0.173	P=0.482
Liver: Hepatocellular Adenoma			
Overall rate	22/49 (45%)	22/50 (44%)	22/50 (44%)
Adjusted rate	46.7%	48.6%	49.2%
Terminal rate	20/41 (49%)	19/35 (54%)	17/34 (50%)
First incidence (days)	456	660	356
Poly-3 test	P=0.448	P=0.511	P=0.490
Liver: Hepatocellular Carcinoma			
Overall rate	9/49 (18%)	9/50 (18%)	13/50 (26%)
Adjusted rate	19.0%	19.6%	29.2%
Terminal rate	4/41 (10%)	4/35 (11%)	7/34 (21%)
First incidence (days)	452	547	537
Poly-3 test	P=0.155	P=0.575	P=0.185
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	29/49 (59%)	27/50 (54%)	30/50 (60%)
Adjusted rate	59.3%	58.4%	65.2%
Terminal rate	22/41 (54%)	21/35 (60%)	21/34 (62%)
First incidence (days)	452	547	356
Poly-3 test	P=0.321	P=0.545N	P=0.352
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	9/49 (18%)	9/50 (18%)	13/50 (26%)
Adjusted rate	19.0%	19.6%	29.2%
Terminal rate	4/41 (10%)	4/35 (11%)	7/34 (21%)
First incidence (days)	452	547	537
Poly-3 test	P=0.155	P=0.575	P=0.185
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	29/49 (59%)	27/50 (54%)	30/50 (60%)
Adjusted rate	59.3%	58.4%	65.2%
Terminal rate	22/41 (54%)	21/35 (60%)	21/34 (62%)
First incidence (days)	452	547	356
Poly-3 test	P=0.321	P=0.545N	P=0.352
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	7/49 (14%)	8/50 (16%)	5/50 (10%)
Adjusted rate	15.1%	17.7%	11.5%
Terminal rate	6/41 (15%)	6/35 (17%)	4/34 (12%)
First incidence (days)	452	621	416
Poly-3 test	P=0.386N	P=0.479	P=0.426N

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

	Vehicle Control	15 mg/kg	30 mg/kg
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	7/49 (14%)	10/50 (20%)	9/50 (18%)
Adjusted rate	15.4%	21.8%	21.1%
Terminal rate	7/41 (17%)	7/35 (20%)	8/34 (24%)
First incidence (days)	729 (T)	547	691
Poly-3 test	P=0.289	P=0.300	P=0.337
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	12/49 (24%)	18/50 (36%)	13/50 (26%)
Adjusted rate	25.9%	38.9%	29.9%
Terminal rate	11/41 (27%)	13/35 (37%)	11/34 (32%)
First incidence (days)	452	547	416
Poly-3 test	P=0.365	P=0.130	P=0.427
Spleen: Hemangiosarcoma			
Overall rate	3/49 (6%)	5/50 (10%)	2/50 (4%)
Adjusted rate	6.6%	11.1%	4.6%
Terminal rate	3/41 (7%)	4/35 (11%)	1/34 (3%)
First incidence (days)	729 (T)	697	468
Poly-3 test	P=0.460N	P=0.348	P=0.524N
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	0/49 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	6.6%	0.0%
Terminal rate	0/41 (0%)	2/35 (6%)	0/34 (0%)
First incidence (days)	—[e]	628	—
Poly-3 test	P=0.604	P=0.117	—[f]
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	3/49 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.6%	0.0%	2.3%
Terminal rate	3/41 (7%)	0/35 (0%)	0/34 (0%)
First incidence (days)	729 (T)	—	606
Poly-3 test	P=0.182N	P=0.122N	P=0.327N
All Organs: Hemangioma			
Overall rate	0/49 (0%)	1/50 (2%)	4/50 (8%)
Adjusted rate	0.0%	2.2%	9.3%
Terminal rate	0/41 (0%)	0/35 (0%)	2/34 (6%)
First incidence (days)	—	709	638
Poly-3 test	P=0.022	P=0.497	P=0.053
All Organs: Hemangiosarcoma			
Overall rate	4/49 (8%)	7/50 (14%)	4/50 (8%)
Adjusted rate	8.8%	15.6%	9.2%
Terminal rate	4/41 (10%)	6/35 (17%)	3/34 (9%)
First incidence (days)	729 (T)	697	468
Poly-3 test	P=0.525	P=0.252	P=0.615
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	4/49 (8%)	8/50 (16%)	8/50 (16%)
Adjusted rate	8.8%	17.8%	18.3%
Terminal rate	4/41 (10%)	6/35 (17%)	5/34 (15%)
First incidence (days)	729 (T)	697	468
Poly-3 test	P=0.129	P=0.170	P=0.156

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

	Vehicle Control	15 mg/kg	30 mg/kg
All Organs: Malignant Lymphoma			
Overall rate	1/49 (2%)	6/50 (12%)	2/50 (4%)
Adjusted rate	2.2%	12.8%	4.6%
Terminal rate	0/41 (0%)	1/35 (3%)	1/34 (3%)
First incidence (days)	695	176	356
Poly-3 test	P=0.376	P=0.060	P=0.482
All Organs: Benign Neoplasms			
Overall rate	28/49 (57%)	30/50 (60%)	32/50 (64%)
Adjusted rate	58.6%	64.4%	69.3%
Terminal rate	25/41 (61%)	23/35 (66%)	24/34 (71%)
First incidence (days)	452	547	356
Poly-3 test	P=0.160	P=0.354	P=0.188
All Organs: Malignant Neoplasms			
Overall rate	24/49 (49%)	29/50 (58%)	25/50 (50%)
Adjusted rate	49.7%	58.9%	52.8%
Terminal rate	17/41 (42%)	15/35 (43%)	15/34 (44%)
First incidence (days)	452	176	356
Poly-3 test	P=0.415	P=0.240	P=0.461
All Organs: Benign or Malignant Neoplasms			
Overall rate	42/49 (86%)	43/50 (86%)	44/50 (88%)
Adjusted rate	85.7%	87.4%	89.2%
Terminal rate	34/41 (83%)	29/35 (83%)	29/34 (85%)
First incidence (days)	452	176	356
Poly-3 test	P=0.353	P=0.520	P=0.411

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm 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 C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	55	55	55
3-Month interim evaluation	5	5	5
Early deaths			
Moribund	3	8	11
Natural deaths	5	7	5
Survivors			
Terminal sacrifice	41	35	34
Missing	1		
Animals examined microscopically	54	55	55
3-Month Interim Evaluation			
Integumentary System			
Skin	(5)	(5)	(5)
Dermis, skin, site of application, inflammation, chronic active		5 (100%)	5 (100%)
Epidermis, skin, site of application, hyperplasia		5 (100%)	5 (100%)
Epidermis, skin, site of application, inflammation, suppurative			1 (20%)
Epidermis, skin, site of application, parakeratosis		1 (20%)	4 (80%)
Sebaceous gland, skin, site of application, hyperplasia		5 (100%)	5 (100%)
Skin, site of application, hyperkeratosis		4 (80%)	4 (80%)
Skin, site of application, ulcer			1 (20%)
Systems Examined with No Lesions Observed			
Alimentary System			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Intestine small, duodenum	(48)	(50)	(50)
Ulcer		1 (2%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		
Peyer's patch, hyperplasia, lymphoid		1 (2%)	1 (2%)

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver	(49)	(50)	(50)
Basophilic focus	4 (8%)	3 (6%)	3 (6%)
Clear cell focus	3 (6%)	3 (6%)	6 (12%)
Clear cell focus, multiple	1 (2%)	4 (8%)	2 (4%)
Eosinophilic focus	7 (14%)	5 (10%)	8 (16%)
Eosinophilic focus, multiple	5 (10%)	4 (8%)	1 (2%)
Infarct	3 (6%)		
Mixed cell focus	3 (6%)	6 (12%)	5 (10%)
Mixed cell focus, multiple	1 (2%)	9 (18%)	5 (10%)
Necrosis	7 (14%)	1 (2%)	9 (18%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	1 (2%)
Bile duct, cyst			1 (2%)
Mesentery	(4)	(4)	(3)
Necrosis, focal			1 (33%)
Fat, necrosis	2 (50%)	3 (75%)	2 (67%)
Pancreas	(49)	(50)	(50)
Basophilic focus		1 (2%)	
Necrosis	1 (2%)		
Duct, cyst		1 (2%)	1 (2%)
Stomach, forestomach	(49)	(50)	(50)
Cyst	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	
Hyperplasia		2 (4%)	1 (2%)
Inflammation, suppurative			1 (2%)
Ulcer		1 (2%)	
Stomach, glandular	(49)	(50)	(50)
Cyst	3 (6%)		1 (2%)
Erosion			1 (2%)
Hyperplasia, focal	1 (2%)		
Inflammation, chronic active			1 (2%)
Mineralization	1 (2%)		2 (4%)
Cardiovascular System			
Heart	(49)	(50)	(50)
Cardiomyopathy			1 (2%)
Necrosis		1 (2%)	
Artery, inflammation, chronic active		1 (2%)	
Endocrine System			
Adrenal cortex	(49)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	5 (10%)
Hypertrophy	22 (45%)	12 (24%)	10 (20%)
Capsule, hyperplasia	11 (22%)	7 (14%)	7 (14%)
Adrenal medulla	(49)	(50)	(50)
Hyperplasia	1 (2%)		2 (4%)
Islets, pancreatic	(49)	(50)	(50)
Hyperplasia	30 (61%)	28 (56%)	26 (52%)
Parathyroid gland	(45)	(42)	(42)
Hyperplasia		1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Endocrine System (continued)			
Pituitary gland	(49)	(47)	(50)
Pars distalis, hyperplasia	1 (2%)		1 (2%)
Thyroid gland	(49)	(50)	(50)
Cyst			1 (2%)
Inflammation, chronic active		1 (2%)	
Follicle, cyst	1 (2%)		
Follicular cell, hyperplasia	8 (16%)	7 (14%)	9 (18%)
General Body System			
None			
Genital System			
Preputial gland	(48)	(50)	(50)
Angiectasis	1 (2%)		
Cyst	17 (35%)	12 (24%)	10 (20%)
Inflammation			1 (2%)
Inflammation, chronic active	5 (10%)	1 (2%)	2 (4%)
Seminal vesicle	(49)	(50)	(50)
Cyst		2 (4%)	
Hypertrophy	1 (2%)		
Testes	(49)	(50)	(50)
Atrophy	1 (2%)	3 (6%)	
Hematopoietic System			
Bone marrow	(49)	(50)	(50)
Hyperplasia	4 (8%)	4 (8%)	6 (12%)
Myelofibrosis		3 (6%)	
Lymph node, mandibular	(48)	(46)	(47)
Hyperplasia, lymphoid	1 (2%)		
Lymph node, mesenteric	(47)	(48)	(48)
Angiectasis	1 (2%)		2 (4%)
Ectasia		1 (2%)	
Hematopoietic cell proliferation		1 (2%)	
Hyperplasia, lymphoid	2 (4%)		
Inflammation, chronic active			1 (2%)
Spleen	(49)	(50)	(50)
Angiectasis		1 (2%)	
Hematopoietic cell proliferation	10 (20%)	12 (24%)	16 (32%)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
Inflammation, chronic active		1 (2%)	
Thymus	(45)	(36)	(39)
Atrophy	5 (11%)		5 (13%)
Epithelial cell, hyperplasia			1 (3%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Integumentary System			
Skin	(49)	(50)	(50)
Hyperkeratosis			2 (4%)
Dermis, skin, site of application, inflammation, chronic active		34 (68%)	50 (100%)
Epidermis, skin, site of application, hyperplasia	1 (2%)	40 (80%)	47 (94%)
Epidermis, skin, site of application, inflammation, suppurative			3 (6%)
Epidermis, skin, site of application, parakeratosis		2 (4%)	8 (16%)
Sebaceous gland, hyperplasia		1 (2%)	
Sebaceous gland, skin, site of application, hyperplasia	1 (2%)	21 (42%)	34 (68%)
Skin, site of application, exudate	1 (2%)	3 (6%)	9 (18%)
Skin, site of application, hyperkeratosis	1 (2%)	38 (76%)	37 (74%)
Skin, site of application, ulcer			7 (14%)
Subcutaneous tissue, edema		1 (2%)	
Musculoskeletal System			
Bone	(49)	(50)	(50)
Hyperostosis			1 (2%)
Nervous System			
None			
Respiratory System			
Lung	(49)	(50)	(50)
Hemorrhage		1 (2%)	
Hyperplasia		3 (6%)	
Alveolar epithelium, hyperplasia	5 (10%)	3 (6%)	8 (16%)
Nose	(49)	(50)	(50)
Lateral wall, inflammation, chronic active	1 (2%)		
Special Senses System			
Eye			(1)
Cornea, degeneration			1 (100%)
Harderian gland	(2)	(1)	(5)
Hyperplasia			1 (20%)
Lacrimal gland			(1)
Mineralization			1 (100%)
Urinary System			
Kidney	(49)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)	
Cyst	3 (6%)	1 (2%)	3 (6%)
Mineralization	37 (76%)	39 (78%)	28 (56%)
Nephropathy	44 (90%)	38 (76%)	38 (76%)
Pigmentation			1 (2%)

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

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

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	55	55	55
3-Month interim evaluation	5	5	5
Early deaths			
Accidental death			1
Moribund	8	12	8
Natural deaths	8	8	6
Survivors			
Terminal sacrifice	34	30	35
Animals examined microscopically	55	55	55

Systems Examined at 3 Months with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Integumentary System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

2-Year Study
Alimentary System

Gallbladder	(46)	(46)	(49)
Intestine large, colon	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)
Leiomyoma		1 (2%)	
Intestine small, jejunum	(50)	(49)	(50)
Liver	(50)	(50)	(50)
Hepatoblastoma	1 (2%)		
Hepatocellular carcinoma	4 (8%)	8 (16%)	7 (14%)
Hepatocellular carcinoma, multiple	1 (2%)	2 (4%)	
Hepatocellular adenoma	12 (24%)	13 (26%)	10 (20%)
Hepatocellular adenoma, multiple	14 (28%)	17 (34%)	18 (36%)
Histiocytic sarcoma	3 (6%)	2 (4%)	1 (2%)
Ito cell tumor benign, multiple		1 (2%)	
Mesentery	(12)	(7)	(9)
Hemangioma			1 (11%)
Sarcoma	1 (8%)		
Pancreas	(49)	(50)	(50)
Histiocytic sarcoma			1 (2%)
Salivary glands	(50)	(50)	(50)

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Stomach, forestomach	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Squamous cell papilloma	2 (4%)	2 (4%)	4 (8%)
Squamous cell papilloma, multiple	1 (2%)		
Stomach, glandular	(50)	(50)	(50)
Sarcoma, metastatic, mesentery	1 (2%)		
Tongue	(1)		
Squamous cell papilloma	1 (100%)		
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)		
Islets, pancreatic	(49)	(50)	(50)
Adenoma	1 (2%)		1 (2%)
Carcinoma		1 (2%)	
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	9 (18%)	6 (12%)	3 (6%)
Pars intermedia, adenoma		3 (6%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)
Follicular cell, adenoma	2 (4%)		
General Body System			
None			
Genital System			
Ovary	(50)	(50)	(50)
Cystadenoma	3 (6%)	2 (4%)	
Granulosa cell tumor benign			1 (2%)
Hemangioma		1 (2%)	1 (2%)
Histiocytic sarcoma	2 (4%)		
Luteoma			1 (2%)
Teratoma benign		2 (4%)	
Periovarian tissue, plasma cell tumor malignant, metastatic, lymph node, mesenteric			1 (2%)
Uterus	(50)	(50)	(50)
Adenocarcinoma	1 (2%)		
Hemangioma		2 (4%)	
Histiocytic sarcoma	2 (4%)	1 (2%)	
Leiomyoma		1 (2%)	
Polyp stromal	1 (2%)	2 (4%)	
Sarcoma stromal	1 (2%)		
Cervix, histiocytic sarcoma	1 (2%)		
Vagina		(1)	

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma			1 (2%)
Lymph node	(2)	(5)	(8)
Lumbar, histiocytic sarcoma	1 (50%)		
Renal, fibrosarcoma, metastatic, skeletal muscle			1 (13%)
Lymph node, mandibular	(49)	(49)	(47)
Hemangioma	1 (2%)		
Plasma cell tumor malignant, metastatic, lymph node, mesenteric			1 (2%)
Lymph node, mesenteric	(49)	(47)	(49)
Plasma cell tumor malignant			1 (2%)
Spleen	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)
Thymus	(41)	(45)	(47)
Integumentary System			
Skin	(50)	(50)	(50)
Fibrosarcoma	1 (2%)	1 (2%)	2 (4%)
Histiocytic sarcoma	1 (2%)		
Pinna, melanoma malignant		1 (2%)	
Skin, site of application, fibrosarcoma	1 (2%)	2 (4%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
Skeletal muscle	(1)		(1)
Fibrosarcoma			1 (100%)
Osteosarcoma	1 (100%)		
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	4 (8%)	6 (12%)
Histiocytic sarcoma	1 (2%)		1 (2%)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)	
Plasma cell tumor malignant, metastatic, lymph node, mesenteric			1 (2%)
Nose	(50)	(50)	(50)

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

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Special Senses System			
Harderian gland	(3)	(2)	
Adenoma	3 (100%)	1 (50%)	
Carcinoma		1 (50%)	
Urinary System			
Kidney	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)
Plasma cell tumor malignant, metastatic, lymph node, mesenteric			1 (2%)
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)	2 (4%)	1 (2%)
Leukemia granulocytic	1 (2%)		
Lymphoma malignant	3 (6%)	9 (18%)	11 (22%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	46	45	36
Total primary neoplasms	77	86	72
Total animals with benign neoplasms	37	40	31
Total benign neoplasms	53	56	46
Total animals with malignant neoplasms	22	23	21
Total malignant neoplasms	24	30	26
Total animals with metastatic neoplasms	4	5	8
Total metastatic neoplasms	4	5	11
Total animals with malignant neoplasms of uncertain primary site		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 Oleic Acid Diethanolamine Condensate: Vehicle Control

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

+: 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 Oleic Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19202	19203	19205	19206	20206	21211	21212	21217	16266	16268	17070	17071	17073	17075	17077	18080	18082	18083	18084	20201	20202	20204	20208	21214	22020	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																										1
Hepatocellular carcinoma													X													4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X		X								X				X		X					X		X		12
Hepatocellular adenoma, multiple		X		X		X			X									X		X	X					14
Histiocytic sarcoma														X												3
Mesentery		+	+												+			+		+	+					12
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma															X											1
Squamous cell papilloma												X		X												2
Squamous cell papilloma, multiple																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Tongue																									+	1
Squamous cell papilloma																									X	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																		X								1
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X	X	X	X				X					X				X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma									X																	2
General Body System																										
None																										

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

Number of Days on Study	1 5 0	4 3 5	4 7 1	5 6 2	5 6 2	5 7 8	6 0 3	6 1 5	6 2 1	6 5 4	6 6 0	6 7 5	6 8 2	6 8 3	7 1 9	7 2 1	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 1 3	1 7 4	2 1 6	1 6 7	2 1 5	1 6 9	2 0 3	2 1 9	2 0 7	1 7 6	1 9 7	1 8 8	2 0 9	2 0 5	1 7 9	2 1 0	1 7 2	1 7 8	1 8 1	1 8 5	1 8 6	1 8 7	1 8 9	1 9 0	1 9 1
Genital System																								
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma	X					X															X			
Histiocytic sarcoma		X	X																					
Oviduct																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Histiocytic sarcoma		X	X																					
Polyp stromal									X															
Sarcoma stromal																		X						
Cervix, histiocytic sarcoma																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Lymph node							+																	
Lumbar, histiocytic sarcoma																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hemangioma																								
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	M	+	+	M	+	M	M	M	+	+	M	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								
Histiocytic sarcoma			X																					
Skin, site of application, fibrosarcoma												X												
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																			
Osteosarcoma					X																			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+						+													
Spinal cord					+						+													
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																
Alveolar/bronchiolar carcinoma						X																		
Hepatocellular carcinoma, metastatic, liver				X										X					X					
Histiocytic sarcoma		X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland									+													+		
Adenoma									X													X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 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 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	7 3 1	7 3 1	
Carcass ID Number	1 9 2	1 9 3	1 9 5	1 9 6	2 0 6	2 1 1	2 1 2	2 1 7	1 6 6	1 6 8	1 7 0	1 7 1	1 7 3	1 7 5	1 7 7	1 8 0	1 8 2	1 8 3	1 8 4	2 0 1	2 0 2	2 0 4	2 0 8	2 1 4	2 2 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										3
Histiocytic sarcoma																										2
Oviduct									+																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																						X				1
Histiocytic sarcoma																										2
Polyp stromal																										1
Sarcoma stromal																										1
Cervix, histiocytic sarcoma														X												1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Lymph node														+												2
Lumbar, histiocytic sarcoma														X												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma			X																							1
Histiocytic sarcoma																										1
Skin, site of application, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma												X									X					3
Hepatocellular carcinoma, metastatic, liver																										3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																+										3
Adenoma																X										3

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

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

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

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19 2	19 3	19 5	19 6	20 6	21 1	21 2	21 7	16 6	16 8	17 0	17 1	17 3	17 5	17 7	18 0	18 2	18 3	18 4	20 1	20 2	20 4	20 8	21 4	22 0	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												3
Leukemia granulocytic																										1
Lymphoma malignant																		X								3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	24 45	24 49	25 00	25 11	25 58	25 59	26 11	26 55	26 68	27 05	27 28	23 11	23 55	23 81	23 89	24 11	24 44	24 47	25 22	25 33	25 54	26 22	26 67	27 00	27 73	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma					X																					1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X															X		X			8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X						X	X					X							X	X			X	13
Hepatocellular adenoma, multiple	X					X	X			X	X	X			X	X	X			X			X			17
Histiocytic sarcoma						X																X				2
Ito cell tumor benign, multiple																										1
Mesentery										+				+				+								7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																					X			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Parathyroid gland	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	M	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X														X			X					X	6
Pars intermedia, adenoma				X																			X			3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma					X																					2
Hemangioma																										1
Teratoma benign																										2
Oviduct																			+							1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	240	445	501	584	585	604	616	624	639	641	646	659	662	667	682	682	704	704	711	730	730	730	730	730
Carcass ID Number	246	229	236	256	255	488	225	230	343	424	433	460	466	434	471	692	723	235	577	727	211	222	266	232	240
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal										X							X								
Vagina																	+								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+					+								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X							
Pinna, melanoma malignant																									
Skin, site of application, fibrosarcoma					X								X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma					X																				
Hepatocellular carcinoma, metastatic, liver												X				X									
Osteosarcoma, metastatic, uncertain primary site															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant											X					X	X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 15 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 4 5	2 4 9	2 5 0	2 5 1	2 5 8	2 5 9	2 6 1	2 6 5	2 6 8	2 7 5	2 8 8	2 8 1	2 3 5	2 3 8	2 3 9	2 4 1	2 4 4	2 4 7	2 5 2	2 5 3	2 5 4	2 6 2	2 6 7	2 7 0	2 7 3	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																					X					2
Histiocytic sarcoma																						X				1
Leiomyoma													X													1
Polyp stromal																										2
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+								+														+			5
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Pinna, melanoma malignant										X																1
Skin, site of application, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																							X			1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Alveolar/bronchiolar carcinoma																X										2
Hepatocellular carcinoma, metastatic, liver						X															X					4
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland													+												+	2
Adenoma													X													1
Carcinoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																X				2
Lymphoma malignant	X		X						X		X	X											X			9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 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 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	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 7	3 2 0	3 2 2	3 2 3	3 2 5	3 2 6	3 2 7	2 7 7	2 7 9	2 8 0	2 8 1	2 8 5	2 8 8	2 9 0	2 9 1	2 9 4	2 9 7	2 9 8	2 9 9	3 0 0	3 0 6	3 1 6	3 2 1	3 2 4	3 3 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Hepatocellular carcinoma	X											X			X										X	7
Hepatocellular adenoma	X											X			X	X								X	X	10
Hepatocellular adenoma, multiple		X		X	X			X	X		X		X	X			X	X				X	X			18
Histiocytic sarcoma																										1
Mesentery				+															+			+			+	9
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																				X					X	4
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	M	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X																					3
Pars intermedia, adenoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Hemangioma																										1
Luteoma				X																						1
Periovarian tissue, plasma cell tumor malignant, metastatic, lymph node, mesenteric					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 mg/kg

Number of Days on Study	369	386	478	524	527	552	604	605	637	659	669	673	692	721	723	730	700	700	730	700	700	730	700	730	730	730
Carcass ID Number	329	308	301	319	276	293	295	305	311	309	307	282	318	310	292	278	283	284	286	296	302	303	312	313	314
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																				
Lymph node							+		+			+							+				+	+		
Renal, fibrosarcoma, metastatic, skeletal muscle									X																	
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant, metastatic, lymph node, mesenteric																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor, malignant																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																				
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																				X						
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																	
Fibrosarcoma									X																	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																		
Spinal cord								+																		
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar adenoma, multiple																										
Alveolar/bronchiolar carcinoma															X									X		
Hepatocellular carcinoma, metastatic, liver										X			X		X											
Histiocytic sarcoma						X																				
Plasma cell tumor malignant, metastatic, lymph node, mesenteric																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																				
Plasma cell tumor malignant, metastatic, lymph node, mesenteric																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 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 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	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 7	3 2 0	3 2 2	3 2 3	3 2 5	3 2 6	3 2 7	2 7 7	2 7 9	2 8 0	2 8 1	2 8 5	2 8 8	2 9 0	2 9 1	2 9 4	2 9 7	2 9 8	2 9 9	3 0 0	3 0 6	3 1 6	3 2 1	3 2 4	3 3 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node									+											+						8
Renal, fibrosarcoma, metastatic, skeletal muscle																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Plasma cell tumor malignant, metastatic, lymph node, mesenteric					X																					1
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Plasma cell tumor malignant					X																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma					X																					2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X												X			X			3
Alveolar/bronchiolar adenoma, multiple									X																	1
Alveolar/bronchiolar carcinoma					X																					3
Hepatocellular carcinoma, metastatic, liver	X														X										X	6
Histiocytic sarcoma																										1
Plasma cell tumor malignant, metastatic, lymph node, mesenteric					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Plasma cell tumor malignant, metastatic, lymph node, mesenteric					X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate: 30 mg/kg

Number of Days on Study	369	386	478	524	527	552	604	605	637	659	669	673	692	721	723	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	329	308	301	319	276	293	295	305	311	319	307	282	318	310	292	278	283	284	286	296	302	303	312	313	314
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 Oleic Acid Diethanolamine Condensate: 30 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	31 7	32 0	32 2	32 3	32 5	32 6	32 7	77 7	79 9	28 0	28 1	28 5	28 8	29 0	29 1	29 4	29 7	29 8	29 9	30 0	30 6	30 6	16 6	21 1	24 1	24	30	Total Tissues/ Tumors
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																												1
Lymphoma malignant												X		X						X					X			11

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

	Vehicle Control	15 mg/kg	30 mg/kg
Harderian Gland: Adenoma			
Overall rate[a]	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate[b]	6.8%	2.3%	0.0%
Terminal rate[c]	2/34 (6%)	1/30 (3%)	0/35 (0%)
First incidence (days)	621	730 (T)	—[e]
Poly-3 test[d]	P=0.060N	P=0.314N	P=0.119N
Harderian Gland: Adenoma or Carcinoma			
Overall rate	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.8%	4.7%	0.0%
Terminal rate	2/34 (6%)	2/30 (7%)	0/35 (0%)
First incidence (days)	621	730 (T)	—
Poly-3 test	P=0.082N	P=0.511N	P=0.119N
Liver: Hepatocellular Adenoma			
Overall rate	26/50 (52%)	30/50 (60%)	28/50 (56%)
Adjusted rate	57.7%	65.5%	63.1%
Terminal rate	20/34 (59%)	21/30 (70%)	24/35 (69%)
First incidence (days)	578	501	659
Poly-3 test	P=0.332	P=0.286	P=0.376
Liver: Hepatocellular Carcinoma			
Overall rate	5/50 (10%)	10/50 (20%)	7/50 (14%)
Adjusted rate	11.3%	22.5%	15.9%
Terminal rate	3/34 (9%)	4/30 (13%)	4/35 (11%)
First incidence (days)	562	585	659
Poly-3 test	P=0.331	P=0.130	P=0.376
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	28/50 (56%)	35/50 (70%)	29/50 (58%)
Adjusted rate	61.4%	74.3%	65.2%
Terminal rate	21/34 (62%)	22/30 (73%)	24/35 (69%)
First incidence (days)	562	501	659
Poly-3 test	P=0.385	P=0.126	P=0.438
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	6/50 (12%)	10/50 (20%)	7/50 (14%)
Adjusted rate	13.4%	22.5%	15.9%
Terminal rate	3/34 (9%)	4/30 (13%)	4/35 (11%)
First incidence (days)	562	585	659
Poly-3 test	P=0.430	P=0.200	P=0.489
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	28/50 (56%)	35/50 (70%)	29/50 (58%)
Adjusted rate	61.4%	74.3%	65.2%
Terminal rate	21/34 (62%)	22/30 (73%)	24/35 (69%)
First incidence (days)	562	501	659
Poly-3 test	P=0.385	P=0.126	P=0.438
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted rate	2.3%	2.3%	9.2%
Terminal rate	0/34 (0%)	1/30 (3%)	4/35 (11%)
First incidence (days)	615	730 (T)	730 (T)
Poly-3 test	P=0.099	P=0.755	P=0.176

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

	Vehicle Control	15 mg/kg	30 mg/kg
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate	6.8%	4.6%	6.9%
Terminal rate	2/34 (6%)	1/30 (3%)	2/35 (6%)
First incidence (days)	578	585	723
Poly-3 test	P=0.585	P=0.507N	P=0.659
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	4/50 (8%)	3/50 (6%)	7/50 (14%)
Adjusted rate	9.0%	6.9%	16.0%
Terminal rate	2/34 (6%)	2/30 (7%)	6/35 (17%)
First incidence (days)	578	585	723
Poly-3 test	P=0.187	P=0.514N	P=0.250
Ovary: Cystadenoma			
Overall rate	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.7%	4.7%	0.0%
Terminal rate	1/34 (3%)	1/30 (3%)	0/35 (0%)
First incidence (days)	150	711	—
Poly-3 test	P=0.087N	P=0.522N	P=0.124N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	9/50 (18%)	6/50 (12%)	3/50 (6%)
Adjusted rate	20.6%	13.8%	6.9%
Terminal rate	8/34 (24%)	4/30 (13%)	3/35 (9%)
First incidence (days)	660	616	730 (T)
Poly-3 test	P=0.043N	P=0.288N	P=0.058N
Pituitary Gland (Pars Intermedia): Adenoma			
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	6.9%	2.3%
Terminal rate	0/34 (0%)	2/30 (7%)	1/35 (3%)
First incidence (days)	—	604	730 (T)
Poly-3 test	P=0.379	P=0.117	P=0.501
Skin: Fibrosarcoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.6%	6.9%	4.6%
Terminal rate	1/34 (3%)	0/30 (0%)	2/35 (6%)
First incidence (days)	675	585	730 (T)
Poly-3 test	P=0.593	P=0.500	P=0.693
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.9%	4.7%	9.2%
Terminal rate	3/34 (9%)	2/30 (7%)	4/35 (11%)
First incidence (days)	730 (T)	730 (T)	730 (T)
Poly-3 test	P=0.418	P=0.507N	P=0.502
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted rate	9.2%	4.7%	9.2%
Terminal rate	4/34 (12%)	2/30 (7%)	4/35 (11%)
First incidence (days)	730 (T)	730 (T)	730 (T)
Poly-3 test	P=0.578N	P=0.344N	P=0.642N

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

	Vehicle Control	15 mg/kg	30 mg/kg
All Organs: Hemangioma			
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.3%	7.0%	4.6%
Terminal rate	1/34 (3%)	2/30 (7%)	2/35 (6%)
First incidence (days)	730 (T)	659	730 (T)
Poly-3 test	P=0.401	P=0.302	P=0.501
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.6%	7.0%	4.6%
Terminal rate	2/34 (6%)	2/30 (7%)	2/35 (6%)
First incidence (days)	730 (T)	659	730 (T)
Poly-3 test	P=0.592N	P=0.496	P=0.693N
All Organs: Histiocytic Sarcoma			
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.7%	4.7%	2.3%
Terminal rate	1/34 (3%)	2/30 (7%)	0/35 (0%)
First incidence (days)	435	730 (T)	552
Poly-3 test	P=0.229N	P=0.523N	P=0.312N
All Organs: Malignant Lymphoma			
Overall rate	3/50 (6%)	9/50 (18%)	11/50 (22%)
Adjusted rate	6.8%	20.7%	24.7%
Terminal rate	1/34 (3%)	6/30 (20%)	7/35 (20%)
First incidence (days)	603	646	604
Poly-3 test	P=0.017	P=0.054	P=0.020
All Organs: Benign Neoplasms			
Overall rate	37/50 (74%)	40/50 (80%)	31/50 (62%)
Adjusted rate	79.7%	85.2%	69.7%
Terminal rate	29/34 (85%)	26/30 (87%)	26/35 (74%)
First incidence (days)	150	501	659
Poly-3 test	P=0.146N	P=0.325	P=0.182N
All Organs: Malignant Neoplasms			
Overall rate	22/50 (44%)	24/50 (48%)	21/50 (42%)
Adjusted rate	46.1%	53.2%	45.8%
Terminal rate	12/34 (35%)	14/30 (47%)	12/35 (34%)
First incidence (days)	435	585	552
Poly-3 test	P=0.538N	P=0.315	P=0.571N
All Organs: Benign or Malignant Neoplasms			
Overall rate	46/50 (92%)	45/50 (90%)	36/50 (72%)
Adjusted rate	92.1%	93.2%	78.5%
Terminal rate	31/34 (91%)	27/30 (90%)	27/35 (77%)
First incidence (days)	150	501	552
Poly-3 test	P=0.028N	P=0.565	P=0.047N

(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, and skin; 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 D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	55	55	55
3-Month interim evaluation	5	5	5
Early deaths			
Accidental death			1
Moribund	8	12	8
Natural deaths	8	8	6
Survivors			
Terminal sacrifice	34	30	35
Animals examined microscopically	55	55	55
3-Month Interim Evaluation			
Genital System			
Ovary	(1)		
Follicle, cyst	1 (100%)		
Integumentary System			
Skin	(5)	(5)	(5)
Dermis, skin, site of application, inflammation, chronic active		4 (80%)	4 (80%)
Epidermis, skin, site of application, hyperplasia		5 (100%)	4 (80%)
Sebaceous gland, skin, site of application, hyperplasia		5 (100%)	5 (100%)
Skin, site of application, hyperkeratosis		2 (40%)	3 (60%)
Systems Examined with No Lesions Observed			
Alimentary System			
Cardiovascular System			
Endocrine System			
General Body System			
Hematopoietic System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Intestine small, duodenum	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)
Intestine small, jejunum	(50)	(49)	(50)
Peyer's patch, hyperplasia	1 (2%)		

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Alimentary System (continued)			
Liver	(50)	(50)	(50)
Angiectasis			1 (2%)
Basophilic focus		1 (2%)	1 (2%)
Clear cell focus	3 (6%)	2 (4%)	3 (6%)
Cyst	1 (2%)	1 (2%)	
Eosinophilic focus	11 (22%)	5 (10%)	10 (20%)
Eosinophilic focus, multiple	4 (8%)	8 (16%)	4 (8%)
Infarct		1 (2%)	
Mixed cell focus	6 (12%)	6 (12%)	6 (12%)
Mixed cell focus, multiple	2 (4%)	2 (4%)	1 (2%)
Necrosis	2 (4%)	1 (2%)	
Pigmentation		1 (2%)	
Vacuolization cytoplasmic			1 (2%)
Bile duct, cyst	1 (2%)		
Mesentery	(12)	(7)	(9)
Inflammation, suppurative			1 (11%)
Necrosis	2 (17%)	2 (29%)	1 (11%)
Fat, necrosis	9 (75%)	5 (71%)	5 (56%)
Pancreas	(49)	(50)	(50)
Basophilic focus		1 (2%)	
Acinus, atrophy			1 (2%)
Duct, cyst	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Hyperkeratosis	1 (2%)	1 (2%)	
Hyperplasia		3 (6%)	
Stomach, glandular	(50)	(50)	(50)
Cyst	1 (2%)		
Inflammation, acute	1 (2%)		
Mineralization			2 (4%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Aorta, mineralization	2 (4%)		
Heart	(50)	(50)	(50)
Degeneration			1 (2%)
Inflammation, suppurative		1 (2%)	
Mineralization	4 (8%)		1 (2%)
Thrombosis		1 (2%)	
Artery, inflammation, chronic active	1 (2%)		
Artery, mineralization	1 (2%)		
Pericardium, inflammation, chronic active	2 (4%)		
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Angiectasis	1 (2%)		
Hyperplasia	1 (2%)		1 (2%)
Hypertrophy	1 (2%)	1 (2%)	
Zona fasciculata, vacuolization cytoplasmic	1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	1 (2%)		2 (4%)
Islets, pancreatic	(49)	(50)	(50)
Hyperplasia	7 (14%)	8 (16%)	6 (12%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Endocrine System (continued)			
Pituitary gland	(50)	(50)	(50)
Angiectasis	4 (8%)		1 (2%)
Hypertrophy	1 (2%)		
Pars distalis, hyperplasia	9 (18%)	6 (12%)	7 (14%)
Thyroid gland	(50)	(50)	(50)
Atrophy		1 (2%)	
Inflammation, chronic active	1 (2%)		
C-cell, hyperplasia	1 (2%)		
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia	14 (28%)	15 (30%)	15 (30%)
General Body System			
None			
Genital System			
Ovary	(50)	(50)	(50)
Angiectasis			1 (2%)
Atrophy	5 (10%)		5 (10%)
Hemorrhage	1 (2%)		
Follicle, cyst	7 (14%)	11 (22%)	14 (28%)
Periovarian tissue, angiectasis	1 (2%)		
Periovarian tissue, cyst			3 (6%)
Oviduct	(1)	(1)	
Atrophy	1 (100%)		
Uterus	(50)	(50)	(50)
Angiectasis		1 (2%)	
Cyst		1 (2%)	
Inflammation, acute	1 (2%)		
Endometrium, hyperplasia			9 (18%)
Endometrium, hyperplasia, cystic	35 (70%)	20 (40%)	28 (56%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hyperplasia	3 (6%)	1 (2%)	2 (4%)
Myelofibrosis	11 (22%)	9 (18%)	8 (16%)
Lymph node	(2)	(5)	(8)
Lumbar, hyperplasia, histiocytic	1 (50%)		
Renal, angiectasis			1 (13%)
Renal, hyperplasia, lymphoid			1 (13%)
Lymph node, mandibular	(49)	(49)	(47)
Hyperplasia		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	2 (4%)	3 (6%)
Lymph node, mesenteric	(49)	(47)	(49)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Spleen	(50)	(50)	(50)
Hematopoietic cell proliferation	22 (44%)	27 (54%)	15 (30%)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	5 (10%)
Thymus	(41)	(45)	(47)
Atrophy	6 (15%)	4 (9%)	5 (11%)
Hyperplasia, lymphoid		2 (4%)	2 (4%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	15 mg/kg	30 mg/kg
2-Year Study (continued)			
Integumentary System			
Mammary gland	(49)	(50)	(49)
Dilatation		1 (2%)	
Hyperplasia, cystic	1 (2%)		
Inflammation, acute	1 (2%)		
Skin	(50)	(50)	(50)
Fibrosis	1 (2%)		
Dermis, skin, site of application, inflammation, chronic active		40 (80%)	49 (98%)
Epidermis, skin, site of application, hyperplasia		43 (86%)	50 (100%)
Epidermis, skin, site of application, parakeratosis			4 (8%)
Sebaceous gland, skin, site of application, hyperplasia		39 (78%)	46 (92%)
Skin, site of application, exudate			6 (12%)
Skin, site of application, hyperkeratosis		36 (72%)	42 (84%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Arthrosis	1 (2%)		
Fibrous osteodystrophy	1 (2%)		2 (4%)
Femur, fibrous osteodystrophy	1 (2%)		
Maxilla, fibrous osteodystrophy	1 (2%)		
Vertebra, fibrous osteodystrophy	1 (2%)		
Nervous System			
Brain	(50)	(50)	(50)
Necrosis			1 (2%)
Respiratory System			
Lung	(50)	(50)	(50)
Hemorrhage			1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)		1 (2%)
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet	3 (6%)	3 (6%)	3 (6%)
Mineralization	9 (18%)	2 (4%)	2 (4%)
Nephropathy	11 (22%)	6 (12%)	16 (32%)
Pigmentation		1 (2%)	
Pelvis, dilatation	1 (2%)		
Renal tubule, dilatation	3 (6%)		

APPENDIX E
GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL 160
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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1988). Oleic acid diethanolamine condensate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 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 oleic acid diethanolamine condensate. The high dose was limited by toxicity.

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). Oleic acid diethanolamine condensate was supplied as a coded aliquot by Radian Corporation. The high dose of oleic acid diethanolamine condensate 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 oleic acid diethanolamine condensate continued for 4 hours, at which time the medium plus oleic acid diethanolamine condensate 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 using freshly prepared S9 from the livers of Aroclor 1254-induced male F344 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 oleic acid diethanolamine condensate 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.

RESULTS

Oleic acid diethanolamine condensate (0.1 to 200 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation enzymes (Table E1; Zeiger *et al.*, 1988). In addition, no induction of TFT resistance was noted in L5178Y mouse lymphoma cells treated with oleic acid diethanolamine condensate in the presence or absence of S9 metabolic activation (Table E2).

TABLE E1
Mutagenicity of Oleic Acid Diethanolamine Condensate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0	115 ± 3.0	75 ± 5.0	91 ± 1.7	83 ± 5.8	139 ± 5.0	87 ± 10.4
	0.1	119 ± 9.0	74 ± 2.9				
	0.3	121 ± 2.8	73 ± 1.5				
	1	121 ± 4.7	74 ± 8.7				
	3.3	116 ± 4.8	70 ± 9.5[c]	99 ± 7.3	80 ± 9.6	142 ± 3.3	82 ± 2.6
	10	131 ± 7.3[c]	55 ± 2.7[c]	107 ± 2.6	87 ± 0.9	118 ± 4.6	91 ± 8.4
	33			106 ± 6.2	82 ± 13.3	119 ± 1.2	91 ± 6.8
	100			101 ± 4.9	85 ± 4.3	99 ± 3.1	89 ± 10.2
	200			74 ± 5.5[c]	81 ± 7.4	35 ± 6.1[c]	79 ± 6.4
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		777 ± 29.8	311 ± 13.0	470 ± 10.3	258 ± 20.2	870 ± 8.2	550 ± 30.1
TA1535	0	32 ± 3.6	8 ± 3.4	18 ± 2.0	5 ± 0.6	18 ± 2.4	7 ± 1.9
	0.1	39 ± 5.1	10 ± 2.2				
	0.3	38 ± 0.6	9 ± 2.4				
	1	32 ± 2.8	10 ± 1.2				
	3.3	39 ± 5.3	7 ± 1.5	18 ± 2.7	5 ± 2.0	14 ± 2.8	7 ± 0.9
	10	31 ± 1.9[c]	9 ± 1.2[c]	16 ± 0.7	8 ± 0.3	15 ± 3.8	8 ± 2.9
	33			15 ± 2.4	4 ± 1.3	17 ± 2.5	4 ± 0.9
	100			13 ± 1.8	8 ± 0.7	17 ± 1.2	6 ± 1.5
	200			14 ± 1.2	6 ± 0.6	7 ± 1.2	8 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		407 ± 12.9	162 ± 4.0	65 ± 0.3	56 ± 5.2	216 ± 2.3	117 ± 12.0
TA97	0	137 ± 6.0	74 ± 3.5	201 ± 17.7	119 ± 2.5	232 ± 12.7	109 ± 7.6
	0.1	128 ± 12.8	76 ± 10.5				
	0.3	136 ± 4.4	58 ± 6.6				
	1	110 ± 0.5	74 ± 3.4				
	3.3	138 ± 7.4	72 ± 2.3[c]	203 ± 6.4	104 ± 7.1	243 ± 4.6	100 ± 2.9
	10	110 ± 4.1[c]	8 ± 3.9[c]	200 ± 5.1	96 ± 12.1	208 ± 0.3	106 ± 6.4
	33			218 ± 15.6	96 ± 6.2	192 ± 4.2	113 ± 5.8
	100			216 ± 11.7	98 ± 3.3	116 ± 5.8	120 ± 5.7
	200			81 ± 7.3[c]	114 ± 4.9	62 ± 5.5[c]	80 ± 1.5[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		413 ± 16.3	1,119 ± 46.4	337 ± 7.4	208 ± 5.6	1,459 ± 70.4	359 ± 4.2

TABLE E1
Mutagenicity of Oleic Acid Diethanolamine Condensate in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA98	0	20 ± 0.3	15 ± 2.0	37 ± 1.0	16 ± 0.7	47 ± 5.4	25 ± 3.1
	0.1	20 ± 1.7	9 ± 2.6				
	0.3	27 ± 3.8	9 ± 3.2				
	1	20 ± 0.7	13 ± 0.6				
	3.3	21 ± 2.9	11 ± 2.9	38 ± 2.5	23 ± 2.8	38 ± 3.2	22 ± 1.2
	10	28 ± 4.9	12 ± 1.5[c]	37 ± 1.9	16 ± 2.7	44 ± 0.9	19 ± 4.4
	33			42 ± 2.1	22 ± 2.5	52 ± 6.1	21 ± 4.4
	100			44 ± 0.9	22 ± 1.5	37 ± 6.0	25 ± 4.5
	200			41 ± 2.3	20 ± 2.0	43 ± 4.0	19 ± 2.1
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		169 ± 5.2	216 ± 12.9	137 ± 6.4	66 ± 2.7	251 ± 4.1	196 ± 16.0

[a] Study was performed at Microbiological Associates, Inc. The detailed protocol and these data are presented by Zeiger *et al.* (1988). 0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), 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 Oleic Acid Diethanolamine Condensate[a]

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Ethanol[c]		107	99	120	38	
		116	95	97	28	
		96	107	116	40	35
Methyl methanesulfonate[d]	5	31	9	709	758	
(μg/mL)		34	11	731	724	
		57	15	639	372	618*
Oleic acid diethanolamine condensate	1.25	111	75	84	25	
(nL/mL)		104	80	137	44	
		115	87	112	33	34
	2.5	98	60	86	29	
		117	63	152	43	
		118	53	109	31	34
	5	110	39	141	43	
		119	56	85	24	
		104	23	139	45	37
	7.5	Lethal				
		Lethal				
		Lethal				
Trial 2						
Ethanol		108	98	87	27	
		116	100	88	25	
		112	88	99	29	
		114	114	95	28	27
Methyl methanesulfonate	5	69	42	682	329	
(μg/mL)		69	47	611	297	
		87	56	668	256	294*
Oleic acid diethanolamine condensate	2	105	75	83	26	
(nL/mL)		107	107	90	28	
		106	100	72	23	26
	3	115	102	59	17	
		116	73	62	18	
		118	140	68	19	18
	4	114	79	89	26	
		112	86	66	20	
		113	117	66	19	22
	6	113	75	72	21	
		117	70	75	21	21
	8	107	46	89	28	
		116	56	81	23	
		107	76	88	27	26
	12	116	81	77	22	
		109	51	71	22	22

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Ethanol		105	36	67	21	
		115	69	81	23	
		120	124	92	26	
		104	170	92	29	25
Methyl methanesulfonate	5	90	70	546	203	
(μg/mL)		87	74	506	194	
		71	20	453	213	203*
Oleic acid diethanolamine condensate	3	98	121	61	21	
(nL/mL)		107	130	78	24	
		103	90	57	18	21
	4	109	107	88	27	
		109	131	66	20	
		110	115	80	24	24
	6	98	45	67	23	
		107	113	87	27	
		105	118	89	28	26
	8	110	60	97	30	
		106	62	69	22	
		100	88	79	26	26
	12	111	50	94	28	
		Lethal				
	15	117	16	112	32	
		118	67	70	20	
		105	59	99	31	28
	20	Lethal				
		Lethal				

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Ethanol		89	78	113	42	
	119	119	128	36		
	116	103	204	59	46	
Methyl cholanthrene[d]	2.5	112	45	986	293	
(μg/mL)		81	44	900	370	
		103	47	998	323	329*
Oleic acid diethanolamine condensate	2.5	93	81	169	60	
(nL/mL)		118	82	230	65	
		107	82	136	42	56
	5	109	115	158	48	
		93	81	151	54	
		113	84	281	83	62
	7.5	102	91	169	55	
		109	103	154	47	51
	10	85	19	134	52	
		89	16	108	40	46
	15	Lethal				
		Lethal				
Trial 2						
Ethanol		76	108	74	33	
		115	77	73	21	
		113	115	85	25	26
		Lethal				
Methyl cholanthrene	2.5	107	68	568	177	
(μg/mL)		68	19	534	262	220*
Oleic acid diethanolamine condensate	2.5	76	22	54	24	
(nL/mL)		114	137	81	24	
		112	80	90	27	25
	5	112	110	56	17	
		85	83	50	20	
		115	108	59	17	18
	7.5	106	93	46	15	
		113	59	91	27	
		108	32	95	29	24
	10	105	85	68	22	
		106	134	74	23	
		111	56	105	32	25
	15	107	46	87	27	
		101	104	66	22	24
		Lethal				
	20	Lethal				
		Lethal				
		Lethal				

* Significant positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. 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

APPENDIX F
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE F1 Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate 168

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10	10	10
Male						
Hematology						
Hematocrit (%)						
Day 5	45.2 ± 0.4	45.8 ± 0.4	45.4 ± 0.5	45.6 ± 0.4	44.7 ± 0.4	46.5 ± 0.4
Day 19	45.8 ± 0.4	46.5 ± 0.7	46.7 ± 0.3	46.3 ± 0.3	46.5 ± 0.6	46.0 ± 0.3
Week 13	48.7 ± 0.2	47.9 ± 0.4	48.7 ± 0.5	48.8 ± 0.4	48.4 ± 0.5	49.1 ± 0.5
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	15.4 ± 0.2	15.2 ± 0.1	15.8 ± 0.2
Day 19	15.9 ± 0.1	16.0 ± 0.2	16.2 ± 0.1	15.9 ± 0.2	16.0 ± 0.2	15.9 ± 0.1
Week 13	16.2 ± 0.1	16.2 ± 0.1	16.0 ± 0.1	16.4 ± 0.2	16.4 ± 0.2	16.6 ± 0.2
Erythrocytes ($10^6/\mu L$)						
Day 5	7.48 ± 0.05	7.62 ± 0.09	7.42 ± 0.08	7.55 ± 0.07	7.41 ± 0.08	7.70 ± 0.07
Day 19	7.99 ± 0.07	8.14 ± 0.14	8.12 ± 0.05	8.07 ± 0.07	8.03 ± 0.12	8.03 ± 0.05
Week 13	8.84 ± 0.03	8.87 ± 0.10	8.90 ± 0.09	9.01 ± 0.08	8.94 ± 0.08	9.09 ± 0.09
Reticulocytes ($10^6/\mu L$)						
Day 5	0.16 ± 0.01	0.17 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.14 ± 0.00	0.16 ± 0.01
Day 19	0.15 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.00	0.14 ± 0.01
Week 13	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.12 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 5	0.05 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02
Day 19	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.02
Week 13	0.02 ± 0.02	0.04 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.05 ± 0.01
Mean cell volume (fL)						
Day 5	60.4 ± 0.2	60.1 ± 0.2	61.1 ± 0.2	60.5 ± 0.2	60.3 ± 0.3	60.4 ± 0.3
Day 19	57.4 ± 0.2	57.2 ± 0.2	57.5 ± 0.2	57.4 ± 0.2	57.9 ± 0.3	57.4 ± 0.1
Week 13	55.1 ± 0.3	54.0 ± 0.2*	54.7 ± 0.2	54.2 ± 0.2	54.2 ± 0.2	54.1 ± 0.2*
Mean cell hemoglobin (pg)						
Day 5	20.5 ± 0.1	20.3 ± 0.2	20.7 ± 0.1	20.4 ± 0.1	20.6 ± 0.1	20.5 ± 0.1
Day 19	19.9 ± 0.1	19.7 ± 0.2	20.0 ± 0.2	19.7 ± 0.1	20.0 ± 0.2	19.8 ± 0.1
Week 13	18.3 ± 0.1	18.3 ± 0.1	18.0 ± 0.1	18.2 ± 0.2	18.4 ± 0.1	18.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.9 ± 0.2	33.7 ± 0.2	33.9 ± 0.1	33.7 ± 0.2	34.1 ± 0.2	34.0 ± 0.2
Day 19	34.8 ± 0.3	34.3 ± 0.3	34.8 ± 0.3	34.3 ± 0.2	34.4 ± 0.3	34.5 ± 0.2
Week 13	33.3 ± 0.2	33.8 ± 0.2	32.9 ± 0.2	33.7 ± 0.3	33.9 ± 0.2	33.9 ± 0.2
Platelets ($10^3/\mu L$)						
Day 5	887.9 ± 14.5	898.5 ± 17.5	923.5 ± 14.4	881.9 ± 17.8	910.2 ± 20.7	881.6 ± 20.9
Day 19	875.9 ± 10.2	881.3 ± 14.4	885.3 ± 18.0	869.7 ± 12.7	824.5 ± 15.9	864.5 ± 16.1
Week 13	722.3 ± 12.6	730.7 ± 21.3	712.6 ± 10.2	749.0 ± 17.4	712.9 ± 8.6	698.7 ± 16.7
Leukocytes ($10^3/\mu L$)						
Day 5	8.42 ± 0.35	8.20 ± 0.21	8.53 ± 0.28	8.41 ± 0.37	8.51 ± 0.40	9.96 ± 0.38*
Day 19	8.85 ± 0.32	8.76 ± 0.43	8.86 ± 0.40	8.92 ± 0.33	9.32 ± 0.39	8.97 ± 0.37
Week 13	9.15 ± 0.44	8.87 ± 0.43	9.23 ± 0.47	8.36 ± 0.46	9.43 ± 0.36	8.67 ± 0.35
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.91 ± 0.11	0.77 ± 0.06	0.94 ± 0.13	0.83 ± 0.10	1.23 ± 0.16	2.22 ± 0.17**
Day 19	1.02 ± 0.09	0.81 ± 0.06	1.07 ± 0.11	1.27 ± 0.08	1.35 ± 0.13	1.39 ± 0.10*
Week 13	1.51 ± 0.09	1.60 ± 0.26	1.39 ± 0.22	1.44 ± 0.22	1.50 ± 0.13	1.91 ± 0.17

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10	10	10
Male (continued)						
Hematology (continued)						
Lymphocytes ($10^3/\mu L$)						
Day 5	7.45 ± 0.28	7.40 ± 0.18	7.53 ± 0.30	7.55 ± 0.36	7.21 ± 0.31	7.65 ± 0.39
Day 19	7.73 ± 0.29	7.87 ± 0.42	7.66 ± 0.40	7.58 ± 0.30	7.89 ± 0.36	7.48 ± 0.37
Week 13	7.45 ± 0.44	7.07 ± 0.28	7.67 ± 0.32	6.69 ± 0.36	7.71 ± 0.34	6.66 ± 0.42
Monocytes ($10^3/\mu L$)						
Day 5	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Day 19	0.04 ± 0.02	0.00 ± 0.00	0.05 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.02
Week 13	0.08 ± 0.04	0.06 ± 0.02	0.07 ± 0.03	0.09 ± 0.03	0.08 ± 0.02	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)						
Day 5	0.05 ± 0.02	0.03 ± 0.02	0.06 ± 0.02	0.02 ± 0.01	0.06 ± 0.03	0.07 ± 0.03
Day 19	0.05 ± 0.02	0.08 ± 0.02	0.08 ± 0.03	0.06 ± 0.02	0.07 ± 0.02	0.06 ± 0.03
Week 13	0.12 ± 0.03	0.13 ± 0.04	0.11 ± 0.04	0.12 ± 0.02	0.14 ± 0.04	0.08 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 5	21.8 ± 0.4	21.7 ± 0.5	21.4 ± 0.6	21.4 ± 0.4	22.1 ± 0.6	21.9 ± 0.5
Day 19	20.8 ± 0.5	20.1 ± 0.7	20.5 ± 0.7	21.1 ± 0.6	22.1 ± 0.6	19.7 ± 0.4
Week 13	23.7 ± 0.3	21.5 ± 0.6*	22.7 ± 0.4	22.5 ± 0.5	23.2 ± 0.4	22.9 ± 0.4
Creatinine (mg/dL)						
Day 5	0.63 ± 0.02	0.69 ± 0.02	0.67 ± 0.02	0.66 ± 0.02	0.68 ± 0.02	0.64 ± 0.02
Day 19	0.64 ± 0.02	0.63 ± 0.02	0.63 ± 0.02	0.64 ± 0.02	0.63 ± 0.02	0.62 ± 0.01
Week 13	0.62 ± 0.01	0.61 ± 0.02	0.64 ± 0.02	0.62 ± 0.01	0.60 ± 0.00	0.60 ± 0.02
Total protein (g/dL)						
Day 5	6.2 ± 0.0	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.0	6.1 ± 0.1	6.3 ± 0.0
Day 19	6.4 ± 0.1	6.3 ± 0.1	6.5 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.2 ± 0.1
Week 13	7.0 ± 0.0	6.9 ± 0.2	7.1 ± 0.1	7.1 ± 0.1	7.0 ± 0.1	6.9 ± 0.1
Albumin (g/dL)						
Day 5	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.1	4.6 ± 0.0
Day 19	4.6 ± 0.0	4.6 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	4.5 ± 0.0
Week 13	4.9 ± 0.0	4.7 ± 0.2	4.9 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	4.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	39 ± 1	40 ± 1	37 ± 1	42 ± 1	40 ± 2	39 ± 1
Day 19	40 ± 2	40 ± 1	39 ± 1	39 ± 1	43 ± 2	40 ± 1
Week 13	51 ± 2	51 ± 4	52 ± 4	49 ± 2	49 ± 1	56 ± 4
Alkaline phosphatase (IU/L)						
Day 5	1,145 ± 15	1,123 ± 18	1,151 ± 20	1,132 ± 24	1,219 ± 23	1,117 ± 23
Day 19	824 ± 19	826 ± 14	844 ± 26	839 ± 20	897 ± 19*	842 ± 19
Week 13	555 ± 10	514 ± 27	506 ± 10	566 ± 14	561 ± 13	662 ± 14**
Sorbitol dehydrogenase (IU/L)						
Day 5	20 ± 1	18 ± 1	18 ± 1	18 ± 1	17 ± 1*	16 ± 1**
Day 19	14 ± 1	14 ± 1	14 ± 1	13 ± 1	14 ± 1	13 ± 1
Week 13	20 ± 1	19 ± 2	20 ± 1[b]	19 ± 1	18 ± 1	18 ± 2
Bile salts (μmol/L)						
Day 5	34.7 ± 4.4	35.8 ± 6.3	31.3 ± 4.6	34.9 ± 5.8	32.6 ± 5.1	35.8 ± 9.5
Day 19	31.8 ± 4.5	27.4 ± 3.4	27.0 ± 2.8	35.5 ± 4.1	20.2 ± 1.4	27.2 ± 3.0
Week 13	24.1 ± 3.3	24.8 ± 1.6	32.6 ± 4.9	21.5 ± 2.5	26.3 ± 3.5	18.8 ± 1.5

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10	10	10
Female						
Hematology						
Hematocrit (%)						
Day 5	47.4 ± 0.3	47.6 ± 0.3	47.2 ± 0.4	46.9 ± 1.0	47.5 ± 0.5	48.3 ± 0.6
Day 19	48.9 ± 0.4	49.6 ± 0.5	48.5 ± 0.6	49.9 ± 0.7	48.4 ± 0.9	49.2 ± 0.8
Week 13	48.7 ± 0.4	48.0 ± 0.5	48.8 ± 0.6	49.0 ± 0.5	47.9 ± 0.2	48.7 ± 0.3
Hemoglobin (g/dL)						
Day 5	15.7 ± 0.1	15.6 ± 0.1	15.7 ± 0.2	15.3 ± 0.2	15.7 ± 0.2	15.9 ± 0.2
Day 19	16.5 ± 0.1	16.6 ± 0.2	16.3 ± 0.2	16.7 ± 0.1	16.4 ± 0.3	16.6 ± 0.2
Week 13	16.1 ± 0.1	15.8 ± 0.1	16.2 ± 0.2	16.3 ± 0.2	16.0 ± 0.2	16.3 ± 0.1
Erythrocytes ($10^6/\mu L$)						
Day 5	7.60 ± 0.06	7.60 ± 0.05	7.53 ± 0.10	7.45 ± 0.17	7.53 ± 0.06	7.66 ± 0.11
Day 19	7.91 ± 0.06	8.04 ± 0.08	7.83 ± 0.10	8.06 ± 0.11	7.81 ± 0.14	7.95 ± 0.13
Week 13	8.19 ± 0.06	8.04 ± 0.09	8.21 ± 0.12	8.25 ± 0.08	8.07 ± 0.04	8.19 ± 0.06
Reticulocytes ($10^6/\mu L$)						
Day 5	0.13 ± 0.01	0.14 ± 0.00	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.01
Day 19	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.10 ± 0.01	0.12 ± 0.01
Week 13	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.09 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 5	0.06 ± 0.02	0.02 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.02 ± 0.01	0.04 ± 0.02
Day 19	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Week 13	0.04 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.03	0.00 ± 0.00**
Mean cell volume (fL)						
Day 5	62.4 ± 0.2	62.7 ± 0.2	62.8 ± 0.3	62.9 ± 0.2	63.1 ± 0.3	63.0 ± 0.2
Day 19	61.8 ± 0.1	61.7 ± 0.2	62.0 ± 0.2	61.9 ± 0.2	62.0 ± 0.2	61.9 ± 0.2
Week 13	59.5 ± 0.1	59.7 ± 0.1	59.5 ± 0.2	59.4 ± 0.1	59.3 ± 0.1	59.6 ± 0.2
Mean cell hemoglobin (pg)						
Day 5	20.6 ± 0.1	20.6 ± 0.1	20.8 ± 0.2	20.6 ± 0.2	20.8 ± 0.1	20.7 ± 0.1
Day 19	20.8 ± 0.1	20.7 ± 0.1	20.9 ± 0.2	20.7 ± 0.2	21.0 ± 0.1	20.9 ± 0.2
Week 13	19.6 ± 0.1	19.7 ± 0.1	19.7 ± 0.1	19.7 ± 0.1	19.8 ± 0.1	19.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.1 ± 0.1	32.9 ± 0.1	33.2 ± 0.2	32.8 ± 0.3	33.0 ± 0.2	32.8 ± 0.2
Day 19	33.7 ± 0.2	33.5 ± 0.1	33.7 ± 0.3	33.5 ± 0.3	33.9 ± 0.2	33.7 ± 0.3
Week 13	33.0 ± 0.2	33.0 ± 0.3	33.2 ± 0.2	33.2 ± 0.3	33.4 ± 0.2	33.5 ± 0.1
Platelets ($10^3/\mu L$)						
Day 5	802.5 ± 15.1	799.3 ± 20.8	784.8 ± 14.2	772.8 ± 18.4	764.5 ± 19.1	819.0 ± 18.9
Day 19	829.6 ± 17.1	812.1 ± 13.0	815.3 ± 14.1	839.7 ± 15.5	811.6 ± 25.0	787.0 ± 19.5
Week 13	701.6 ± 13.0	748.0 ± 11.8	735.3 ± 11.4	706.8 ± 18.2	742.3 ± 8.8	731.2 ± 15.0
Leukocytes ($10^3/\mu L$)						
Day 5	8.20 ± 0.58	7.53 ± 0.39	7.90 ± 0.40	7.43 ± 0.35	8.44 ± 0.64	10.13 ± 0.67
Day 19	7.51 ± 0.36	7.76 ± 0.20	7.24 ± 0.19	7.62 ± 0.33	7.94 ± 0.40	7.52 ± 0.36
Week 13	6.35 ± 0.25	6.46 ± 0.21	7.47 ± 0.31*	6.86 ± 0.34	6.96 ± 0.32	8.36 ± 0.62**
Segmented neutrophils ($10^3/\mu L$)						
Day 5	1.01 ± 0.13	0.89 ± 0.13	0.91 ± 0.05	0.74 ± 0.08	1.13 ± 0.10	1.87 ± 0.23**
Day 19	0.86 ± 0.11	0.83 ± 0.07	0.83 ± 0.08	0.83 ± 0.06	1.22 ± 0.07**	1.12 ± 0.11*
Week 13	1.15 ± 0.10	1.14 ± 0.15	1.25 ± 0.11	1.24 ± 0.23	1.99 ± 0.27*	2.61 ± 0.42**
Lymphocytes ($10^3/\mu L$)						
Day 5	7.12 ± 0.49	6.61 ± 0.34	6.90 ± 0.38	6.64 ± 0.33	7.24 ± 0.60	8.14 ± 0.51
Day 19	6.57 ± 0.34	6.72 ± 0.25	6.26 ± 0.18	6.68 ± 0.32	6.60 ± 0.38	6.26 ± 0.30
Week 13	5.05 ± 0.23	5.10 ± 0.22	6.06 ± 0.28	5.45 ± 0.30	4.75 ± 0.22	5.60 ± 0.35

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10	10	10
Female (continued)						
Hematology (continued)						
Monocytes ($10^3/\mu L$)						
Day 5	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.02
Day 19	0.04 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.04 ± 0.01	0.07 ± 0.02	0.04 ± 0.01
Week 13	0.05 ± 0.02	0.07 ± 0.01	0.08 ± 0.02	0.08 ± 0.03	0.05 ± 0.03	0.07 ± 0.03
Eosinophils ($10^3/\mu L$)						
Day 5	0.06 ± 0.03	0.03 ± 0.02	0.09 ± 0.02	0.05 ± 0.02	0.05 ± 0.03	0.10 ± 0.03
Day 19	0.04 ± 0.02	0.15 ± 0.03*	0.09 ± 0.02	0.08 ± 0.02	0.05 ± 0.02	0.10 ± 0.03
Week 13	0.11 ± 0.03	0.15 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.16 ± 0.03	0.09 ± 0.03
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 5	24.2 ± 0.6	24.5 ± 0.7	23.8 ± 0.9	22.6 ± 0.7	24.5 ± 0.8	22.7 ± 0.9
Day 19	22.0 ± 0.5	22.4 ± 0.6	22.0 ± 0.3[b]	21.8 ± 0.6	21.5 ± 0.3	21.8 ± 0.5
Week 13	24.6 ± 0.4	24.5 ± 0.5	25.3 ± 0.7	25.7 ± 0.7	26.0 ± 0.8	25.5 ± 0.5
Creatinine (mg/dL)						
Day 5	0.70 ± 0.02	0.66 ± 0.02	0.70 ± 0.02	0.68 ± 0.01	0.69 ± 0.02	0.63 ± 0.02*
Day 19	0.68 ± 0.01	0.68 ± 0.01	0.70 ± 0.02[b]	0.67 ± 0.02	0.67 ± 0.02	0.65 ± 0.02
Week 13	0.68 ± 0.02	0.67 ± 0.02	0.64 ± 0.02	0.67 ± 0.02	0.64 ± 0.01	0.66 ± 0.02
Total protein (g/dL)						
Day 5	5.8 ± 0.0	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1
Day 19	6.1 ± 0.1	6.0 ± 0.1	6.0 ± 0.1[b]	6.1 ± 0.1	6.1 ± 0.1	6.1 ± 0.1
Week 13	7.1 ± 0.1	6.9 ± 0.1	7.0 ± 0.1	7.1 ± 0.1	6.9 ± 0.1	7.1 ± 0.1
Albumin (g/dL)						
Day 5	4.4 ± 0.0	4.3 ± 0.0	4.4 ± 0.0	4.3 ± 0.0	4.4 ± 0.0	4.2 ± 0.1
Day 19	4.5 ± 0.0	4.5 ± 0.0	4.4 ± 0.1[b]	4.5 ± 0.1	4.5 ± 0.1	4.6 ± 0.1
Week 13	5.0 ± 0.1	4.9 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	34 ± 1	35 ± 1	34 ± 1	35 ± 1	35 ± 1	36 ± 2
Day 19	33 ± 1	35 ± 1	34 ± 1[b]	35 ± 1	37 ± 1**	39 ± 1**
Week 13	45 ± 3	42 ± 1	44 ± 2	45 ± 1	49 ± 2	51 ± 3
Alkaline phosphatase (IU/L)						
Day 5	931 ± 26	979 ± 26	973 ± 35	966 ± 22	935 ± 21	947 ± 21
Day 19	802 ± 20	821 ± 26	786 ± 15[b]	823 ± 25	786 ± 16	887 ± 28
Week 13	529 ± 16	527 ± 13	517 ± 9	554 ± 15	584 ± 18**	631 ± 29**
Sorbitol dehydrogenase (IU/L)						
Day 5	23 ± 1	20 ± 1*	18 ± 1**	21 ± 1*	20 ± 1*	17 ± 1**
Day 19	16 ± 1	16 ± 1	16 ± 1	17 ± 1	17 ± 1	17 ± 1
Week 13	21 ± 1	17 ± 1	17 ± 1	18 ± 1	16 ± 1*	18 ± 2
Bile salts (μmol/L)						
Day 5	32.0 ± 4.2	33.6 ± 2.9	28.1 ± 5.0	26.7 ± 3.8	25.8 ± 3.1	27.8 ± 4.5
Day 19	33.0 ± 5.7	40.2 ± 5.5	32.7 ± 5.1[b]	39.6 ± 8.3	40.4 ± 5.8	28.7 ± 5.6
Week 13	28.5 ± 2.0	28.8 ± 4.1	29.1 ± 1.9	25.0 ± 2.4	26.1 ± 4.9	25.6 ± 1.9

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

APPENDIX G
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate 174
TABLE G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate 175

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10	10	10
Male						
Necropsy body wt	357 ± 5	360 ± 6	356 ± 7	353 ± 7	333 ± 5*	295 ± 9**
Heart						
Absolute	1.063 ± 0.014	1.099 ± 0.015	1.088 ± 0.012	1.051 ± 0.024	1.053 ± 0.021	0.998 ± 0.014*
Relative	2.98 ± 0.04	3.06 ± 0.05	3.06 ± 0.06	2.98 ± 0.05	3.16 ± 0.06*	3.40 ± 0.07**
R. Kidney						
Absolute	1.332 ± 0.022	1.349 ± 0.033	1.366 ± 0.026	1.359 ± 0.029	1.361 ± 0.023	1.251 ± 0.030
Relative	3.73 ± 0.02	3.74 ± 0.05	3.84 ± 0.05	3.85 ± 0.08	4.08 ± 0.05**	4.25 ± 0.07**
Liver						
Absolute	15.365 ± 0.543	15.280 ± 0.364	14.703 ± 0.403	15.215 ± 0.426	14.708 ± 0.369	13.220 ± 0.458**
Relative	42.98 ± 1.08	42.42 ± 0.69	41.23 ± 0.60	43.10 ± 1.03	44.16 ± 1.12	44.80 ± 0.77
Lung						
Absolute	1.872 ± 0.044	1.912 ± 0.074	1.877 ± 0.049	1.968 ± 0.086	1.913 ± 0.085	1.663 ± 0.072
Relative	5.26 ± 0.15	5.31 ± 0.20	5.29 ± 0.18	5.59 ± 0.26	5.74 ± 0.24	5.64 ± 0.20
R. Testis						
Absolute	1.475 ± 0.016	1.498 ± 0.029	1.522 ± 0.018	1.476 ± 0.026	1.482 ± 0.019	1.413 ± 0.020
Relative	4.14 ± 0.04	4.16 ± 0.05	4.28 ± 0.06	4.18 ± 0.03	4.45 ± 0.07**	4.82 ± 0.11**
Thymus						
Absolute	0.317 ± 0.011	0.331 ± 0.011	0.314 ± 0.010	0.336 ± 0.020	0.273 ± 0.012	0.241 ± 0.022**
Relative	0.89 ± 0.04	0.92 ± 0.03	0.88 ± 0.03	0.96 ± 0.06	0.82 ± 0.04	0.81 ± 0.06
Female						
Necropsy body wt	193 ± 5	196 ± 5	198 ± 4	191 ± 3	189 ± 3	185 ± 4
Heart						
Absolute	0.685 ± 0.017	0.698 ± 0.011	0.708 ± 0.010	0.697 ± 0.012	0.688 ± 0.012	0.701 ± 0.015
Relative	3.55 ± 0.07	3.58 ± 0.06	3.58 ± 0.06	3.65 ± 0.08	3.64 ± 0.06	3.79 ± 0.07
R. Kidney						
Absolute	0.758 ± 0.017	0.786 ± 0.017	0.791 ± 0.020	0.783 ± 0.016	0.812 ± 0.019*	0.821 ± 0.016*
Relative	3.93 ± 0.07	4.02 ± 0.07	4.00 ± 0.10	4.09 ± 0.05	4.29 ± 0.06**	4.44 ± 0.08**
Liver						
Absolute	7.573 ± 0.197	7.621 ± 0.277	8.023 ± 0.219	7.713 ± 0.112	7.775 ± 0.166	7.723 ± 0.207
Relative	39.19 ± 0.56	38.90 ± 0.74	40.60 ± 1.05	40.35 ± 0.58	41.11 ± 0.84	41.68 ± 0.54*
Lung						
Absolute	1.341 ± 0.049	1.281 ± 0.018	1.210 ± 0.036	1.262 ± 0.049	1.214 ± 0.026*	1.202 ± 0.030*
Relative	6.95 ± 0.23	6.59 ± 0.21	6.12 ± 0.16**	6.58 ± 0.20	6.42 ± 0.13	6.49 ± 0.12
Thymus						
Absolute	0.250 ± 0.007	0.249 ± 0.011	0.252 ± 0.006	0.234 ± 0.009	0.221 ± 0.009*	0.211 ± 0.015**
Relative	1.30 ± 0.04	1.27 ± 0.05	1.28 ± 0.03	1.22 ± 0.05	1.17 ± 0.04	1.14 ± 0.08*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	9	10	10	10	10	9
Necropsy body wt	37.6 ± 1.0	38.2 ± 0.8	37.0 ± 0.9	36.5 ± 0.7	35.8 ± 0.6	33.4 ± 0.6**
Heart						
Absolute	0.170 ± 0.004	0.182 ± 0.005	0.183 ± 0.006	0.174 ± 0.003	0.199 ± 0.010*	0.185 ± 0.005*
Relative	4.54 ± 0.13	4.76 ± 0.14	4.97 ± 0.17	4.79 ± 0.09	5.59 ± 0.30**	5.54 ± 0.14**
R. Kidney						
Absolute	0.332 ± 0.008	0.378 ± 0.006**	0.378 ± 0.013**	0.366 ± 0.008	0.370 ± 0.010*	0.364 ± 0.009
Relative	8.86 ± 0.21	9.93 ± 0.19**	10.24 ± 0.31**	10.04 ± 0.17**	10.35 ± 0.18**	10.90 ± 0.14**
Liver						
Absolute	1.818 ± 0.062	1.971 ± 0.043*	1.979 ± 0.032*	1.959 ± 0.054*	1.996 ± 0.041*	2.084 ± 0.051**
Relative	48.32 ± 0.83	51.62 ± 0.67*	53.71 ± 0.89**	53.70 ± 1.08**	55.88 ± 1.06**	62.35 ± 0.81**
Lung						
Absolute	0.240 ± 0.007	0.266 ± 0.010	0.251 ± 0.007	0.259 ± 0.007	0.263 ± 0.013	0.241 ± 0.008
Relative	6.42 ± 0.27	6.98 ± 0.31	6.82 ± 0.20	7.11 ± 0.21	7.38 ± 0.40	7.22 ± 0.20
R. Testis						
Absolute	0.117 ± 0.002	0.129 ± 0.001*	0.121 ± 0.004	0.123 ± 0.004	0.125 ± 0.002	0.115 ± 0.003
Relative	3.11 ± 0.08	3.38 ± 0.09	3.27 ± 0.10	3.39 ± 0.13*	3.50 ± 0.04**	3.44 ± 0.05*
Thymus						
Absolute	0.047 ± 0.002	0.045 ± 0.002	0.043 ± 0.004	0.038 ± 0.003*	0.039 ± 0.002*	0.037 ± 0.003*
Relative	1.25 ± 0.05	1.17 ± 0.05	1.17 ± 0.10	1.04 ± 0.07	1.10 ± 0.06	1.12 ± 0.07
Female						
n	10	10	10	10	10	10
Necropsy body wt	32.2 ± 1.2	32.7 ± 0.6	33.2 ± 0.8	31.1 ± 0.7	30.4 ± 0.6	30.9 ± 0.4
Heart						
Absolute	0.136 ± 0.004	0.150 ± 0.004*	0.156 ± 0.008**	0.156 ± 0.003**	0.158 ± 0.004**	0.167 ± 0.002**
Relative	4.29 ± 0.19	4.60 ± 0.11	4.71 ± 0.23	5.02 ± 0.13**	5.21 ± 0.09**	5.42 ± 0.10**
R. Kidney						
Absolute	0.227 ± 0.005	0.249 ± 0.005	0.251 ± 0.004	0.290 ± 0.042	0.260 ± 0.005	0.273 ± 0.007
Relative	7.10 ± 0.19	7.63 ± 0.16	7.59 ± 0.23	9.27 ± 1.23*	8.57 ± 0.10*	8.83 ± 0.21*
Liver						
Absolute	1.500 ± 0.057	1.711 ± 0.049**	1.770 ± 0.037**	1.731 ± 0.051**	1.832 ± 0.053**	1.977 ± 0.039**
Relative	46.88 ± 1.81	52.28 ± 1.02**	53.41 ± 1.01**	55.68 ± 1.17**	60.25 ± 1.23**	64.00 ± 0.98**
Lung						
Absolute	0.228 ± 0.011	0.249 ± 0.013	0.252 ± 0.011	0.257 ± 0.017	0.232 ± 0.005	0.240 ± 0.007
Relative	7.17 ± 0.45	7.59 ± 0.35	7.61 ± 0.36	8.34 ± 0.68	7.63 ± 0.15	7.78 ± 0.25
Thymus						
Absolute	0.058 ± 0.003	0.052 ± 0.002	0.057 ± 0.002	0.053 ± 0.003	0.047 ± 0.002**	0.047 ± 0.002**
Relative	1.80 ± 0.06	1.60 ± 0.06	1.73 ± 0.07	1.69 ± 0.09	1.54 ± 0.06	1.54 ± 0.07*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

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TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10
Weights (g)				
Necropsy body wt	357 ± 5	353 ± 7	333 ± 5*	295 ± 9**
L. cauda epididymis	0.1615 ± 0.0065	0.1660 ± 0.0044	0.1722 ± 0.0027	0.1679 ± 0.0034
L. epididymis	0.4464 ± 0.0059	0.4562 ± 0.0079	0.4626 ± 0.0092	0.4468 ± 0.0048
L. testis	1.5314 ± 0.0171	1.5389 ± 0.0268	1.5227 ± 0.0138	1.4725 ± 0.0216
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.84 ± 0.30	9.60 ± 0.19	9.79 ± 0.17	9.96 ± 0.21
Spermatid heads (10^7/testis)	15.07 ± 0.50	14.77 ± 0.33	14.90 ± 0.27	14.67 ± 0.38
Spermatid count (mean/10^{-4} mL suspension)	75.33 ± 2.51	73.83 ± 1.65	74.50 ± 1.35	73.33 ± 1.92
Epididymal spermatozoal measurements				
Motility (%)	65.81 ± 1.94	67.87 ± 1.50	64.10 ± 1.47	65.96 ± 2.08
Concentration (10^6/g cauda epididymal tissue)	694 ± 51	595 ± 49	640 ± 34	562 ± 34

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

TABLE H2
Summary of Estrous Cycle Characterization for Female Rats in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10
Necropsy body wt (g)	193 ± 4	191 ± 3	189 ± 3	185 ± 4
Estrous cycle length (days)	4.90 ± 0.10	5.25 ± 0.31	5.00 ± 0.00	5.00 ± 0.00
Estrous stages (% of cycle)				
Diestrus	39.2	38.3	37.5	39.2
Proestrus	17.5	10.8	17.5	19.2
Estrus	25.8	33.3	27.5	23.3
Metestrus	17.5	17.5	17.5	18.3

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
n	9	10	10	9
Weights (g)				
Necropsy body wt	37.6 ± 1.0	36.5 ± 0.7	35.8 ± 0.6	33.4 ± 0.6**
L. cauda epididymis	0.0161 ± 0.0008	0.0158 ± 0.0007	0.0140 ± 0.0009	0.0137 ± 0.0005
L. epididymis	0.0453 ± 0.0009	0.0463 ± 0.0018	0.0434 ± 0.0010	0.0407 ± 0.0013
L. testis	0.1149 ± 0.0017	0.1199 ± 0.0040	0.1193 ± 0.0023	0.1132 ± 0.0038
Spermatid measurements				
Spermatid heads (10^7/g testis)	20.03 ± 0.59	20.08 ± 0.45	19.76 ± 0.38	20.25 ± 0.39
Spermatid heads (10^7/testis)	2.30 ± 0.07	2.40 ± 0.08	2.36 ± 0.05	2.29 ± 0.06
Spermatid count (mean/10^{-4} mL suspension)	71.86 ± 2.11	75.05 ± 2.59	73.63 ± 1.69	71.44 ± 1.96
Epididymal spermatozoal measurements				
Motility (%)	69.19 ± 3.04	65.96 ± 1.53	66.32 ± 2.29	62.22 ± 3.36
Concentration (10^6/g cauda epididymal tissue)	1,036 ± 78	994 ± 67	1,076 ± 69	1,147 ± 112

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test
[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

TABLE H4
Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Dermal Study of Oleic Acid Diethanolamine Condensate[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
n	10	10	10	10
Necropsy body wt (g)	32.2 ± 1.2	31.1 ± 0.7	30.4 ± 0.6	30.9 ± 0.4
Estrous cycle length (days)	4.20 ± 0.13	4.80 ± 0.48	4.05 ± 0.05	4.25 ± 0.11
Estrous stages (% of cycle)				
Diestrus	26.7	30.0	30.8	33.3
Proestrus	20.8	20.0	19.2	17.5
Estrus	30.8	30.0	29.2	27.5
Metestrus	21.7	20.0	20.8	21.7

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Oleic Acid Diethanolamine Condensate

Oleic acid diethanolamine condensate was obtained from Henkel Corporation, Emery Group (Cincinnati, OH) in one lot (1H01722285), which was used during the 13-week and 2-year studies. Identity and purity analyses were conducted by the study laboratory. Stability studies were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the oleic acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear liquid, was identified as oleic acid diethanolamine condensate by infrared spectroscopy. The spectrum was consistent with that expected for the structure, with the spectrum of an additional lot of oleic acid diethanolamine condensate (CH1F980, Rhône-Poulenc, Inc., Louisville, KY) not used in the current studies, and with the spectrum of a lot (DA-021, ONX Chemical Company, Blue Island, IL) previously analyzed by Midwest Research Institute (1978). The infrared spectrum is presented in Figure I1.

The purity of lot 1H01722285 was determined by high-performance liquid chromatography (HPLC). Solutions were prepared in methanol (10 and 20 mg/mL), and samples were analyzed by HPLC with a Phenomenex Ultramex 3 C_{18} column with two mobile phases: (A) water:methanol (20:80) and (B) methanol. The solvent flow rate was 0.55 mL/minute, and the solvent program was 100:0 to 56:44 A:B in a linear gradient over 45 minutes with a final hold of 25 minutes; ultraviolet detection was at 230 nm. HPLC revealed a major peak and 16 smaller peaks with areas of 0.5% or less relative to the major peak area. The oleic acid diethanolamine condensate content was 47.5%.

The impurities in lot 1H01722285 were further analyzed by HPLC/mass spectrometry. The HPLC system was the same as that used for the purity analysis; peaks were identified by particle beam transport in the chemical ionization mode with methane mass spectrometry. Impurities were identified as other fatty acid alkanolamides (approximately 30%) and remaining peaks were either other fatty acids or unidentified organic impurities. ThermedeTec, Inc. (Woburn, MA), analyzed polar and nonpolar nitrosamines using HPLC with a thermo-energy analyzer. Nitrosodiethanolamine was identified at a concentration of 68 ppb. No nonpolar nitrosamines were found (detection limits: volatile nitrosamines, 10 ppb; nonvolatile nitrosamines, 80 ppb). Free diethanolamine was estimated at 0.19% based on the amine value supplied by the manufacturer.

Stability studies were performed by the analytical chemistry laboratory on lot DA-021 by gas chromatography with 3% SP-2100 on a 100/120 Supelcoport glass column with flame ionization detection; the oven temperature program was 220° C for 2 minutes, then 220° to 300° C at 8° C per minute. A nitrogen carrier gas at a flow rate of 70 mL/minute was used. Docosane (1.24 mg/mL chloroform) was used as an internal standard. Samples were diluted with methanol, the internal standard was added, and the samples were dried under a nitrogen stream. Bis(trimethylsilyl) trifluoroacetamide with 1% trimethylchlorosilane was added, and the samples were swirled and heated to 60° C for 30 minutes before being analyzed with gas chromatography. Results indicated that oleic acid diethanolamine condensate was stable when stored up to 2 weeks at 25° C. Samples stored at 60° C were not stable. The bulk chemical was stored in amber glass bottles with Teflon®-lined lids, protected from light, at room temperature throughout the studies. Stability was monitored at the end of the 13-week studies and throughout the 2-year studies with the HPLC system described for the purity analyses. No degradation of bulk chemical was detected.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY) in eleven lots. The purity was monitored by the study laboratory throughout the studies by gas chromatography with a flame ionization detector. The column 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 standards were analyzed concomitantly. In comparison to the reference standard, purity of the bulk ethanol ranged from 97% to 103% except for one sample taken during the 2-year studies, which measured 110%. The result for this sample was considered to be spurious because analysis of the same material approximately 2 months later indicated a relative purity of 101%. No volatile impurities were detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by mixing oleic acid diethanolamine condensate with 95% ethanol to give the desired concentration (Table I1). The dose formulations were stored at room temperature, protected from light, in amber glass bottles for up to 28 days.

Stability studies of a 10 mg/mL formulation prepared from lot CH1F980 were performed by the study laboratory using HPLC as described for purity analyses but with a solvent program of 100:0 to 20:80 A:B in a linear gradient over 45 minutes, with a hold for 5 minutes, and then an increase to 100:0 A:B in 1 minute. Stability of the dose formulation was confirmed for at least 28 days when stored in sealed containers, protected from ultraviolet light, at up to room temperature or for 3 hours when stored open to air and light.

Periodic analyses of the dose formulations of oleic acid diethanolamine condensate were conducted at the study laboratory using HPLC. During the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies (Table I2). All of the dose formulations and animal room samples analyzed for rats and mice were within 10% of the target concentration. During the 2-year studies, dose formulations were analyzed approximately every 9 weeks (Table I3). For rats, 92% (22/24) of the dose formulations were within 10% of the target concentration; the two formulations that were not within 10% were remixed, analyzed, and found to be within specification. All dose formulations for mice and all animal room samples for rats and mice were within 10% of the target concentrations.

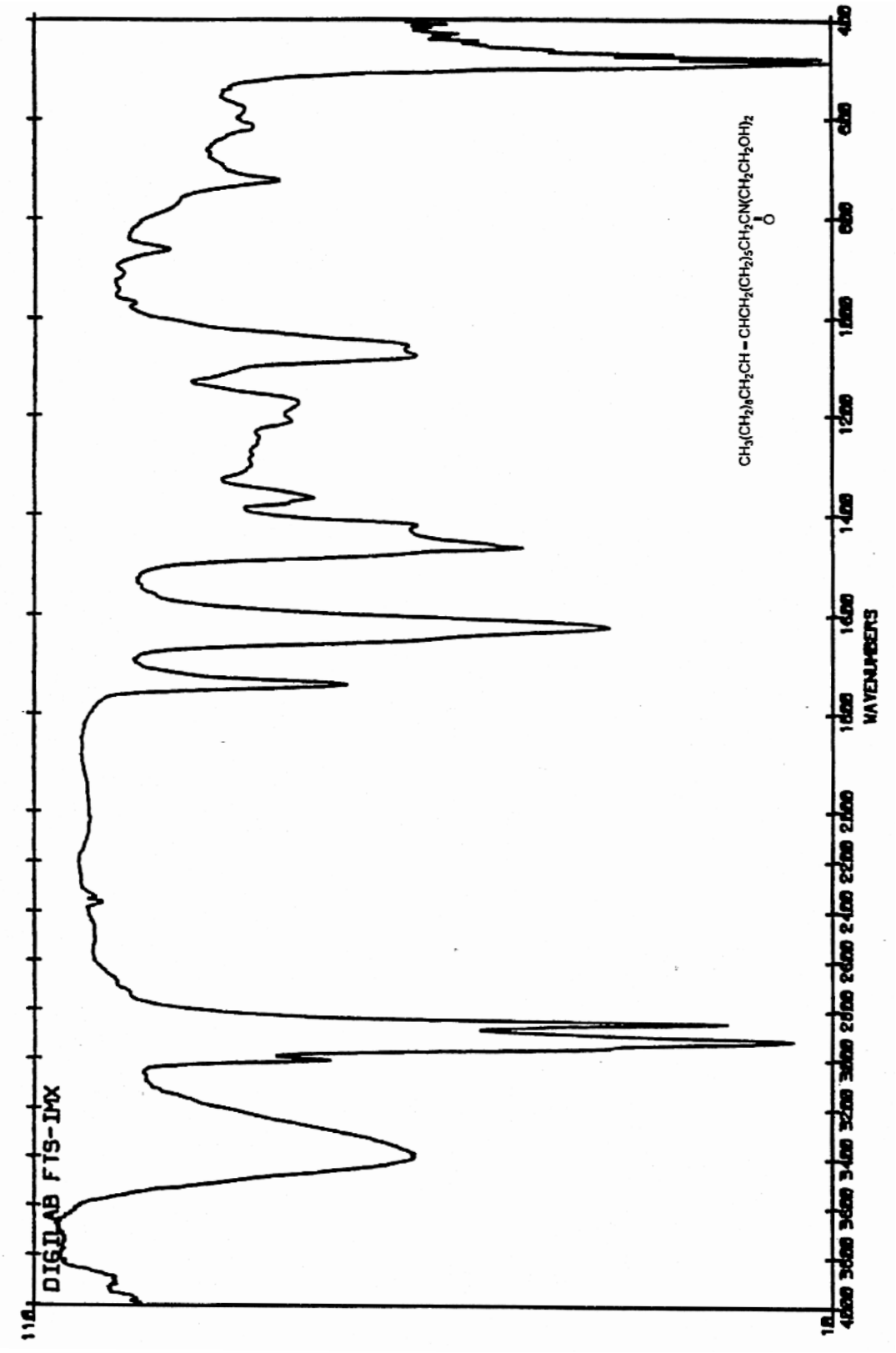

FIGURE I1
Infrared Absorption Spectrum of Oleic Acid Diethanolamine Condensate

TABLE I1
Preparation and Storage of Dose Formulations in the 13-Week and 2-Year Dermal Studies of Oleic Acid Diethanolamine Condensate

Preparation	Doses were prepared by weighing the appropriate amount of diethanolamine and mixing it by stirring or sonicating with 95% ethanol. Doses were prepared every 3 weeks.
Chemical Lot Number	1H01722285
Maximum Storage Time	28 days
Storage Conditions	Stored in amber glass bottles at room temperature, protected from ultraviolet light
Study Laboratory	Battelle Columbus Laboratories (Columbus, OH)

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of Oleic Acid Diethanolamine Condensate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
12 June 1992	12-14 June 1992	30	30.0	0
		61	61.6	+1
		121	119	2
		243	248	+2
		485	490	+1
	13 July 1992[b]	30	29.2	-3
		61	60.4	1
		121	123	+2
		243	248	+2
		485	471	3
24 July 1992	25-27 July 1992	30	31.4	+5
		61	66.4	+9
		121	127	+5
		243	259	+7
		485	510	+5
	25-28 August 1992[b]	30	30.7	+2
		61	61.9	+1
		121	117	3
		243	249	+2
		485	499	+3
4 September 1992	4-6 September 1992	30	30.3	+1
		61	60.3	1
		121	123	+2
		243	248	+2
		485	490	+1
	28-30 September 1992[b]	30	30.2	+1
		61	60.7	0
		121	122	+1
		243	246	+1
		485	489	+1
Mice				
12 June 1992	12-14 June 1992	20	19.8	1
		40	39.9	0
		80	81.1	+1
		160	164	+3
		320	321	0
	13 July 1992[b]	20	19.6	2
		40	41.0	+3
		80	78.1	2
		160	159	1
		320	310	3

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of Oleic Acid Diethanolamine Condensate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
24 July 1992	25-27 July 1992	20	20.6	+3
		40	43.2	+8
		80	86.1	+8
		160	174	+9
		320	337	+5
	25-28 August 1992[b]	20	20.1	+1
		40	39.6	1
		80	84.2	+5
		160	162	+1
		320	328	+3
4 September 1992	4-6 September 1992	20	20.1	+1
		40	41.0	+3
		80	80.9	+1
		160	165	+3
		320	333	+4
	28-30 September 1992[b]	20	20.6	+3
		40	40.2	+1
		80	81.7	+2
		160	166	+4
		320	328	+3

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 155 to 298 μL (males) and 111 to 162 μL (females); 30 mg/mL=25 mg/kg, 61 mg/mL=50 mg/kg, 121 mg/mL=100 mg/kg, 243 mg/mL=200 mg/kg, and 485 mg/mL=400 mg/kg. For mice, dosing volumes ranged from 66 to 97 μL (males) and 54 to 83 μL (females); 20 mg/mL=50 mg/kg, 40 mg/mL=100 mg/kg, 80 mg/mL=200 mg/kg, 160 mg/mL=400 mg/kg, 320 mg/mL=800 mg/kg.
[b] Animal room samples

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Oleic Acid Diethanolamine Condensate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats			
3 May 1993	85	80.7	5
	170	162	5
3 May 1993[b]	85	82.7	3
	170	164	4
6 July 1993	85	82.8	3
	170	175	+3
7 September 1993	85	80.0	6
	170	163	4
8 November 1993	85	88.8	+4
	170	182	+7
8 November 1993[b]	85	85.2	0
	170	172	+1
11 January 1994	85	73.8	13
	170	134	21
14 January 1994	85	90.4[c]	+6
	170	176[c]	+4
14 March 1994	85	81.0	5
	170	168	1
16 May 1994	85	83.3	2
	170	176[d]	+4
16 May 1994[b]	85	90.9	+7
	170	178	+5
19 July 1994	85	90.3	+6
	170	176	+4
19 September 1994	85	88.0	+4
	170	180	+6
21 November 1994	85	86.2	+1
	170	171	+1
21 November 1994[b]	85	89.9	+6
	170	177	+4
26 January 1995	85	87.1	+2
	170	181	+6
27 March 1995	85	87.4	+3
	170	179	+5

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Oleic Acid Diethanolamine Condensate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice			
3 May 1993	7.5	6.8	9
	15	14.1	6
3 May 1993[b]	7.5	7.1	5
	15	14.8	1
6 July 1993	7.5	7.2	4
	15	15.0	0
7 September 1993	7.5	7.2	4
	15	14.7	2
8 November 1993	7.5	7.6	+1
	15	16.1	+7
8 November 1993[b]	7.5	7.5	0
	15	15.3	+2
11 January 1994	7.5	8.1	+8
	15	15.7	+5
14 March 1994	7.5	7.7	+3
	15	14.5	3
16 May 1994	7.5	7.6	+1
	15	16.2	+8
16 May 1994[b]	7.5	8.0	+7
	15	16.2	+8
19 July 1994	7.5	7.4	1
	15	14.7	2
19 September 1994	7.5	7.6	+1
	15	16.5	+10
21 November 1994	7.5	7.8	+4
	15	15.2	+1
21 November 1994[b]	7.5	7.9	+5
	15	15.9	+6
26 January 1995	7.5	7.8	+4
	15	15.5	+3

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Oleic Acid Diethanolamine Condensate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)			
27 March 1995	7.5	8.0	+7
	15	16.4	+9

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 76 to 272 μL (males) and 63 to 166 μL (females); 85 mg/mL=50 mg/kg, 170 mg/mL=100 mg/kg. For mice, dose volumes ranged from 46 to 101 μL (males) and 38 to 112 μL (females); 7.5 mg/mL=15 mg/kg, 15 mg/mL=30 mg/kg.
[b] Animal room samples
[c] Results of remix
[d] Mean of four analyses

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

TABLE J1	Ingredients of NIH-07 Rat and Mouse Ration	192
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TABLE J1
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 J2
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.94 ± 0.47	22.1 — 23.6	26
Crude fat (% by weight)	5.36 ± 0.18	5.00 — 5.80	26
Crude fiber (% by weight)	3.15 ± 0.28	2.60 — 4.00	26
Ash (% by weight)	6.27 ± 0.16	5.72 — 6.64	26
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)	6,727 ± 564	5,500 — 8,800	26
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)	17.20 ± 3.46	14.0 — 26.0	25
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 ± 0.06	1.03 — 1.33	26
Phosphorus (%)	0.89 ± 0.03	0.840 — 0.970	26
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 J4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.16	0.10 — 0.80	26
Cadmium (ppm)	0.05 ± 0.02	0.04 — 0.13	26
Lead (ppm)	0.23 ± 0.06	0.20 — 0.40	26
Mercury (ppm)	<0.02		26
Selenium (ppm)	0.34 ± 0.10	0.10 — 0.50	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[c]	7.48 ± 2.70	2.90 — 14.0	26
Nitrite nitrogen (ppm)[c]	1.36 ± 0.88	0.30 — 3.50	26
BHA (ppm)[d]	1.27 ± 1.82	0.01 — 10.0	26
BHT (ppm)[d]	1.71 ± 1.10	0.18 — 5.00	26
Aerobic plate count (CFU/g)	129,808 ± 132,027	13,000 — 460,000	26
Coliform (MPN/g)	138 ± 548	3 — 2,800	26
Escherichia coli (MPN/g)	6.5 ± 3.6	3.00 — 10.0	26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[e]	12.30 ± 3.94	4.0 — 23.0	26
N-Nitrosodimethylamine (ppb)[e]	10.60 ± 3.70	3.0 — 21.0	26
N-Nitrosopyrrolidine (ppb)[e]	1.70 ± 0.76	1.0 — 4.0	26
Pesticides (ppm)			
α-BHC	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.10		26
Estimated PCBs	<0.20		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.12 ± 0.16	0.02 — 0.83	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

[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] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 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 blood was collected during the studies are also listed.

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

Method and Test	Time of Analysis
MICE	
13-Week Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
K (Papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM	1, 6, 12, and 18 months, study termination
GDVII	1, 6, 12, and 18 months, study termination
LCM	1, 6, 12, and 18 months
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
LCM	18 months and study termination
MCMV	Study termination
Mouse adenoma virus-FL	Study termination
Hemagglutination Inhibition	
K	1, 6, 12, and 18 months, study termination
MVM	1, 6, 12, and 18 months, study termination
Polyoma virus	1, 6, 12, and 18 months, study termination

RESULTS

Five rats and seven mice had positive titers for *M. arthritidis* at study termination. 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. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.