NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

LAURIC ACID DIETHANOLAMINE CONDENSATE

(CAS NO. 120-40-1)

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 480

NIH Publication No. 99-3970

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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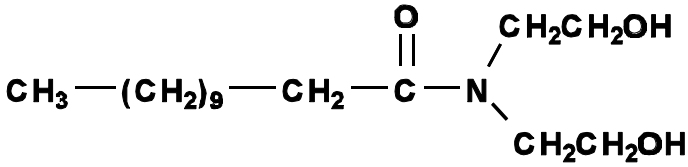
ABSTRACT



LAURIC ACID DIETHANOLAMINE CONDENSATE

CAS No. 120-40-1

Chemical Formula: $C_{16}H_{33}NO_3$ Molecular Weight: 287.50

Synonyms: N,N-bis(2-hydroxyethyl) dodecanamide; N,N-bis(hydroxyethyl) lauramide; N,N-bis(β-hydroxyethyl) lauramide; bis(2-hydroxyethyl) lauramide; coco diethanolamide; coconut oil amide of diethanolamine; diethanollauramide; N,N-diethanollauramide; N,N-diethanollauric acid amide; lauramide DEA; lauric diethanolamide; lauroyl diethanolamide; lauryl diethanolamide; LDA; LDE

Trade names: Clindrol 200 L; Ninol AA62; Onyxol 345; Rewomid DLMS; Rewomid DL 203/S; Richamide 6310; Rolamid CD; Standamidd LD; Steinamid DL 203 S; Super amide L-9A; Super amide L-9C; Synotol L-60; Unamide J-56; Varamid ML 1

Lauric acid diethanolamine condensate is widely used in cosmetics, shampoos, soaps, and related consumer products, to which there is extensive human exposure. Because of the lack of information about potential risks associated with long-term exposure, lauric acid diethanolamine condensate, coconut oil acid diethanolamine condensate, and oleic acid diethanolamine condensate were selected as representative of the class of diethanolamides for evaluation of prechronic toxicity and carcinogenic potential. Male and female F344/N rats and B6C3F$_1$ mice were exposed to lauric acid diethanolamine condensate dermally for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were administered 0, 25, 50, 100, 200, or 400 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 14 weeks. All animals survived until study termination. Final mean body weights and body weight gains of males receiving 200 or 400 mg/kg were significantly less than those of the vehicle control group. Irritation of the skin at the site of application was observed in males receiving 100 mg/kg or greater and in females receiving 200 or 400 mg/kg. Kidney weights of females administered 200 or 400 mg/kg were significantly greater than those of the vehicle control group. There were dose-dependent increases in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, chronic inflammation, parakeratosis, and ulcer.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were administered 0, 50, 100, 200, 400, or 800 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 14 weeks. All animals survived until the end of the study, and final mean body weights and body weight gains of dosed mice were generally similar to those of the vehicle control

groups. Irritation of the skin at the site of application was observed in all males and females administered 400 or 800 mg/kg. The kidney weights of males receiving 100, 400, or 800 mg/kg and females receiving 800 mg/kg were significantly greater than those of the vehicle controls. Liver weights of females administered 200 mg/kg or greater were significantly greater than those of vehicle controls. Increased incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, chronic inflammation, parakeratosis, and ulcer, were observed in males and females receiving 200 mg/kg or greater.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were administered 0, 50, or 100 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 104 or 105 weeks.

Survival and Body Weights

There were no significant differences between vehicle control and dosed males or females in survival or mean body weights.

Pathology Findings

There were no chemical-related differences in neoplasm incidences. Dose-related increases occurred in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, hyperkeratosis, chronic inflammation, parakeratosis, and ulcer.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were administered 0, 100, or 200 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 105 or 106 weeks.

Survival and Body Weights

There were no significant differences in survival between vehicle control and dosed males or females. Mean body weights of females that received 200 mg/kg were less than those of the vehicle controls beginning at week 33.

Pathology Findings

The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in dosed females compared to the vehicle controls, as was the incidence of hepatocellular adenoma in the 100 mg/kg female group. There were dose-related increases in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, hyperkeratosis, chronic inflammation, and parakeratosis. Dosed males had greater incidences of thyroid gland follicular cell focal hyperplasia than did the vehicle controls.

GENETIC TOXICOLOGY

Lauric acid diethanolamine condensate was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation enzymes. No increase in the frequency of mutant colonies of L5178Y mouse lymphoma cells was noted after exposure to lauric acid diethanolamine condensate, with or without S9. In cytogenetic tests with cultured Chinese hamster ovary cells, lauric acid diethanolamine condensate was shown to induce sister chromatid exchanges, but not chromosomal aberrations, with and without S9. *In vivo*, no increase in the frequency of micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male and female mice treated dermally with lauric acid diethanolamine condensate for 14 weeks.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of lauric acid diethanolamine condensate in male or female F344/N rats administered 50 or 100 mg/kg or in male B6C3F$_1$ mice administered 100 or 200 mg/kg. There was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms. These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate.

Dermal administration of lauric acid diethanolamine condensate to rats and mice for 2 years resulted in increased incidences of epidermal and sebaceous

gland hyperplasia, hyperkeratosis, chronic inflammation, and parakeratosis at the site of application. Lauric acid diethanolamine condensate administration also resulted in increased incidences of thyroid gland follicular cell hyperplasia in dosed male mice.

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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 Lauric 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, 100, or 200 mg/kg	0, 100, or 200 mg/kg
Body weights	Dosed groups similar to vehicle control group	Dosed groups similar to vehicle control group	Dosed groups similar to vehicle control group	200 mg/kg group less than vehicle control group
Survival rates	12/50, 18/50, 16/50	28/50, 26/50, 22/50	40/50, 37/50, 41/50	37/50, 40/49, 29/50
Nonneoplastic effects	Skin (site of application): epidermal hyperplasia (0/50, 29/50, 44/50); sebaceous gland hyperplasia (0/50, 27/50, 44/50); hyperkeratosis (0/50, 23/50, 25/50); chronic inflammation (0/50, 10/50, 28/50); parakeratosis (0/50, 21/50, 33/50); ulcer (0/50, 4/50, 25/50)	Skin (site of application): epidermal hyperplasia (5/50, 33/50, 44/50); sebaceous gland hyperplasia (3/50, 41/50, 45/50); hyperkeratosis (0/50, 20/50, 29/50); chronic inflammation (3/50, 35/50, 34/50); parakeratosis (2/50, 12/50, 25/50); ulcer (3/50, 2/50, 10/50)	Skin (site of application): epidermal hyperplasia (4/50, 45/50, 50/50); sebaceous gland hyperplasia (1/50 45/50, 48/50); hyperkeratosis (3/50, 45/50, 49/50); chronic inflammation (1/50, 13/50, 28/50); parakeratosis (0/50, 1/50, 5/50) Thyroid gland: follicular cell hyperplasia (18/50, 24/50, 36/50)	Skin (site of application): epidermal hyperplasia (0/50, 42/49, 50/50); sebaceous gland hyperplasia (0/50, 43/49, 45/50); hyperkeratosis (4/50, 41/49, 48/50); chronic inflammation (0/50, 24/49, 40/50); parakeratosis (0/50, 3/49, 9/50)
Neoplastic effects	None	None	None	Liver: hepatocellular adenoma (23/50, 32/49, 29/50); hepatocellular adenoma or carcinoma (combined) (28/50, 40/49, 36/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	Some evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9			
Mouse lymphoma gene mutations:	Negative with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on lauric 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 carcinogenicity studies of lauric acid diethanolamine condensate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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

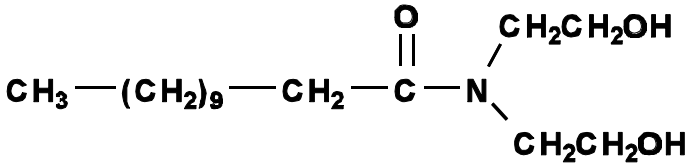
Dr. Hecht, a principal reviewer, agreed with the proposed conclusions. As in the case of the Technical Report on coconut oil acid diethanolamine condensate, he felt that the scientific conclusions were clouded by the use of a mixture with such a large amount of diethanolamine as a contaminant, uncertainty about the actual concentration of the nitrosodiethanolamine impurity, and the confounding issue of the considerable spontaneous incidence of mouse liver neoplasms.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions with the provision that the last sentence of the conclusions for carcinogenicity be amended to indicate the association of the neoplasms with the free diethanolamine in the condensate.

Dr. Bailer, the third principal reviewer, agreed with the proposed conclusions. He said he had some specific questions relating to the logistic model used such as whether the fit had been quantified, why the comparisons were made using survival, and what was the sensitivity of the model to the assumed amounts of diethanolamine in the various condensates. Dr. J.K. Haseman, NIEHS, said he would consider adding a goodness of fit statistic or a graphical display to the relevant table which would show how well the predicted and observed values agreed (Figure 5, page 47). Dr. Bailer noted many organ/tissue sites outlined in the text with trend test P values of 0.03 to 0.07 and wondered how it was decided which trends should be highlighted. He noted especially Zymbal's gland neoplasms in male rats for which he thought the findings might support *equivocal evidence*. Dr. J.R. Hailey, NIEHS, responded that in the case of the Zymbal's gland, one of the three neoplasms reported was determined not to be of Zymbal's gland origin. Dr. Irwin said that biological plausibility or meaningfulness also comes into consideration with borderline cases.

Dr. Goldsworthy moved that the Technical Report on lauric acid diethanolamine condensate be accepted with the revisions discussed and the conclusions as written, *no evidence of carcinogenic activity* in male and female rats and male mice, and *some evidence of carcinogenic activity* in female mice. The last sentence of the conclusions for carcinogenicity would be changed, as for the coconut oil acid diethanolamine condensate Technical Report, to read: "These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate." Dr. Bailer seconded the motion, which was accepted by seven votes with one abstention (Dr. Bus).

INTRODUCTION



LAURIC ACID DIETHANOLAMINE CONDENSATE

CAS No. 120-40-1

Chemical Formula: $C_{16}H_{33}NO_3$ Molecular Weight: 287.50

Synonyms: N,N-bis(2-hydroxyethyl) dodecanamide; N,N-bis(hydroxyethyl) lauramide; N,N-bis(β-hydroxyethyl) lauramide; bis(2-hydroxyethyl) lauramide; coco diethanolamide; coconut oil amide of diethanolamine; diethanollauramide; N,N-diethanollauramide; N,N-diethanollauric acid amide; lauramide DEA; lauric diethanolamide; lauroyl diethanolamide; lauryl diethanolamide; LDA; LDE

Trade names: Clindrol 200 L; Ninol AA62; Onyxol 345; Rewomid DLMS; Rewomid DL 203/S; Richamide 6310; Rolamid CD; Standamidd LD; Steinamid DL 203 S; Super amide L-9A; Super amide L-9C; Synotol L-60; Unamide J-56; Varamid ML 1

CHEMICAL AND PHYSICAL PROPERTIES

Lauric acid diethanolamine condensate is prepared by the condensation of lauric acid methyl ester with diethanolamine at elevated temperature and in the presence of a catalyst. Lauric acid diethanolamine condensate may exist as a viscous light yellow liquid or a white to light yellow, waxy solid with a melting point ranging from 37° to 47° C. Lauric acid diethanolamine condensate is not soluble in water, but it is dispersible in water and produces an alkaline aqueous dispersion (CTFA, 1985).

PRODUCTION, USE, AND HUMAN EXPOSURE

Fatty acid diethanolamides, including lauric acid diethanolamine condensate, are widely used in cosmetics. Lauric acid diethanolamine condensate is present in over 600 cosmetic formulations of bath additives, shampoos, conditioners, lipsticks, and hair dyes. In these formulations, the concentration of diethanolamide may range from 1% to 25%. Non-cosmetic applications include use as a surfactant in bar soaps, light duty detergents, and dishwashing detergents (CTFA, 1985). The National Occupational Exposure Survey estimated that 792,310 workers were occupationally exposed to lauric acid diethanolamine condensate during 1981 through 1983 (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Lauric acid, the 12-carbon, fatty acid portion of lauric acid diethanolamine condensate, is metabolized directly by β-oxidation with successive removal of two carbon (acetyl) fragments from the carboxyl terminal end of the molecule (Lehninger, 1982). It may also be metabolized by a route involving hydroxylation of its twelfth (ω) carbon atom by certain cytochrome $P_{450}4A$ isoforms followed by oxidation of the ω hydroxyl group to a carboxylic acid by cytosolic alcohol and aldehyde dehydrogenases. The resulting 12-carbon dicarboxylic acid is then degraded by

β-oxidation (Mortensen, 1992; Castle *et al.*, 1995; Lake and Lewis, 1996).

A number of observations now suggest that lauric acid diethanolamine condensate also may be metabolized in a similar pathway involving an initial ω-hydroxylation. Following oral administration to rats, lauric acid diethanolamine condensate was rapidly metabolized, and short-chain carboxylic acids were excreted in the urine (Mathews *et al.*, 1996), consistent with a degradative pathway of biotransformation of lauric acid diethanolamine condensate to a carboxylic acid which then undergoes β-oxidation.

Merdink *et al.* (1996) found that incubation of lauric acid diethanolamine condensate with rat liver microsomes resulted in greater than 97% conversion to the 11- or 12- hydroxyl derivative. Incubation with microsomes from rats treated with di-(2-ethylhexyl)-phthalate, a cytochrome P_{450}4A inducer, led to a fivefold increase in the specific activity of carbon 12 hydroxylation with no change in the specific activity of 11-hydroxylation, suggesting that different isoforms were involved in the 11- and 12-hydroxylation reactions. In the presence of a polyclonal antibody to rat cytochrome P_{450}4A isoforms, 12-hydroxylation by rat liver microsomes was inhibited by 80%, while 11-hydroxylation was unaffected. Merdink *et al.* (1996) demonstrated that lauric acid diethanolamine condensate was also hydroxylated on carbon 11 or 12 by human liver microsomes.

These results are consistent with a degradation pathway in which the first step is hydroxylation on carbon 12 (ω hydroxylation) by an inducible form of cytochrome P_{450}4A. The ω hydroxyl group is then oxidized to an ω carboxyl group by cytosolic alcohol and aldehyde dehydrogenases (Boleda *et al.*, 1993), and the resulting fatty acid diethanolamine condensate is degraded by β-oxidation.

Mathews *et al.* (1996) examined the absorption, metabolism, and disposition of ^{14}C-lauric acid diethanolamide in 3-month-old F344/N rats and B6C3F_1 mice. Following intravenous administration of 25 mg/kg to rats, lauric acid diethanolamide was rapidly distributed and eliminated. Approximately 50% of the dose was eliminated in urine during the first 6 hours and over 80% was eliminated in urine during the first 24 hours. Excretion of volatiles was negligible and only a small fraction (7%) appeared in the feces. After 72 hours, approximately 3% of the dose was recovered in tissues, with tissue to blood ratios highest for adipose tissue and liver. Following oral administration to rats (1,000 mg/kg), lauric acid diethanolamide was well absorbed and rapidly eliminated; more than 60% of the dose was eliminated in urine and 4% in feces during the first 24 hours, and 80% was eliminated in the urine and 9% in feces after 72 hours. Lauric acid diethanolamide was well absorbed following oral administration to mice and was rapidly distributed to tissues, metabolized, and eliminated after oral or intravenous administration. Approximately 95% of the dose was eliminated during the first 24 hours, with 90% appearing in the urine.

After oral or intravenous administration, the plasma concentration of lauric acid diethanolamide declined rapidly with the concomitant appearance of circulating polar metabolites. Analysis of urine collected during the first 6 hours after dosing revealed that greater than 90% of the lauric acid diethanolamide equivalents were present as two major metabolites, identified as the half amides of succinic and adipic acid. No parent compound, diethanolamine, or diethanolamine-derived metabolites were detected even after an oral dose of 1,000 mg/kg, indicating that the amide linkage to diethanolamine is not cleaved during metabolism. These half amides were also the major metabolites identified in human and rat liver slices incubated with lauric acid diethanolamide. Additional minor metabolites corresponding to ω-1 to ω-4 hydroxy lauric acid diethanolamide were also detected in liver slice incubations.

Mathews *et al.* (1996) also examined dermal absorption in rats and mice. Absorption through rat skin was slow, with less than 26% of the dose penetrating during the first 72 hours, whereas in mice, 50% to 70% of the applied dose was absorbed in the first 72 hours. Repeated dermal applications (5 days per week for 3 weeks) did not change the rate of absorption or the disposition in rats or mice. However, comparison of the percentage of applied dose excreted when the application site was protected with an appliance to the percentage excreted without an appliance indicated that the vast majority of dermally administered material was ingested orally during grooming. Analysis of lauric acid diethanolamide equivalents present in blood and plasma of cannulated rats during dermal administration revealed approximately 15% was present as parent compound, with the

remainder being the half amides of succinic and adiptic acid. No diethanolamine or diethanolamine-derived metabolites were detected.

Humans

No information on the absorption, distribution, metabolism, or excretion of lauric acid diethanolamine condensate in humans was found in the literature.

TOXICITY

Experimental Animals

No information on the dermal toxicity of lauric acid diethanolamine condensate was found in the literature. In rats, the oral LD_{50} of a 25% solution of lauric acid diethanolamine condensate in corn oil is greater than 5 g/kg; for a 10% emulsion in water, the LD_{50} is 2.7 g/kg. A 50% solution of lauric acid diethanolamine condensate in corn oil was classified as nontoxic by percutaneous absorption (CTFA, 1985).

Gaunt *et al*. (1967) administered diets containing 0, 0.1%, 0.5%, 1.0%, or 2.0% lauric acid diethanolamine to groups of 15 male and 15 female weanling Carworth Farm E rats for 90 days. There were no treatment-related deaths. Mean body weights of males and females receiving diets containing 0.5% or greater were reduced throughout the study; however, this appeared to be due to reduced feed consumption by these groups rather than a treatment-related toxic response. Mean absolute kidney weights were increased in female rats that received diets containing 0.5% or greater lauric acid diethanolamine condensate, and aspartate aminotransferase activity was slightly increased in the same groups. There were no treatment-related differences in hematology, urinalysis, or clinical chemistry parameters; organ weights; or gross observations. Based on these results, the authors concluded that the no-effect-level for dietary exposure was 0.1%.

In studies commissioned by the Monsanto Company (1969), lauric acid diethanolamine condensate was administered dermally to groups of 20 male and 20 female Wistar rats at doses of 0, 25, 80, or 250 mg/kg for 13 weeks or in feed to groups of four male and four female beagle dogs at concentrations of 0, 500, 1,600, or 5,000 ppm for 12 weeks. Body weights and feed consumption were recorded weekly, and clinical chemistry and hematology parameters were measured after 6 and 12 weeks of chemical exposure. At necropsy, animals received a complete gross examination; organ weights were recorded for the adrenal gland, cecum (rats only), heart, kidney, liver, ovary, pituitary gland, spleen, testis, and thyroid gland, and tissues were collected for microscopic examination. No deaths occurred during either study, and no treatment-related differences were observed.

Humans

No information on the toxicity of lauric acid diethanolamine condensate in humans was found in the literature.

CARCINOGENICITY

No information on the carcinogenicity of lauric acid diethanolamine condensate in animals or humans was found in the literature.

GENETIC TOXICITY

Lauric acid was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537, and lauric acid diethanolamine condensate was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, when tested with or without exogenous metabolic activation (S9) (Zeiger *et al.*, 1988). Lauric acid diethanolamine condensate did not induce chromosomal aberrations in cultured Chinese hamster ovary cells whether treated with or without S9 (Loveday *et al.*, 1990). However, lauric acid diethanolamine condensate did increase the frequencies of sister chromatid exchanges in cultured Chinese hamster ovary cells incubated both in the presence and the absence of S9 (Loveday *et al.*, 1990).

STUDY RATIONALE

Lauric acid diethanolamine condensate is widely used in cosmetics, shampoos, soaps, and related consumer products to which there is extensive human exposure. Typically, these products are 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, lauric acid diethanolamine condensate, coconut oil acid diethanolamine condensate, and oleic acid diethanolamine condensate were selected by the National Cancer Institute as representative 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

Lauric Acid Diethanolamine Condensate

Lauric acid diethanolamine condensate was obtained from Rhone Poulenc, Inc. (Louisville, KY), in one lot (CH1E952). 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 lauric acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

The purity of lot CH1E952 was determined by high-performance liquid chromatography (HPLC) and nitrosamine quantitation. HPLC indicated one major peak and four smaller impurity peaks with areas of 0.5% or greater relative to the major peak area. One impurity peak appeared to have multiple components. The HPLC data and manufacturer's data indicated a purity of approximately 90% for lauric acid diethanolamine condensate, with approximately 5% amine (probably diethanolamine) and approximately 5% other organic impurities. One polar nitrosamine, nitrosodiethanolamine, was detected at a concentration of 3,600 ppb. No nonpolar nitrosamines were detected.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory on lot DS42578CG by gas chromatography. Lauric acid diethanolamine condensate showed some instability when stored in glass vials for 2 weeks at 60° C but very little at 25° C or less. Stability was monitored during the 14-week and 2-year studies using HPLC. No degradation of the bulk chemical was detected. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in amber glass bottles sealed with Teflon®-lined caps.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY) in 11 lots. Lot 91D22U was used in the 14-week studies and at the beginning of the 2-year studies; the remaining lots were used throughout the 2-year studies. The purity of the 95% ethanol used in the 14-week and 2-year studies was monitored at the beginning and 2 weeks after the end of the 14-week studies and every 2 to 4 months during the 2-year studies using gas chromatography. USP/NF ethanol reference standards were examined concomitantly. Purity of the bulk ethanol ranged from 97% to 103% relative to the reference standard, 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%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by liquefying and stirring lauric acid diethanolamine condensate at approximately 70° C. A weighed amount of lauric acid diethanolamine condensate was mixed with approximately half the required 95% ethanol, and the mixture was sonicated until it appeared to be in solution. The solution was allowed to cool and was then diluted to volume with 95% ethanol to give the proper concentration (Table I1). The dose formulations were stored in sealed containers at room temperature, protected from light, for up to 28 days.

Stability studies of the 10 mg/mL dose formulation were performed by the study laboratory using HPLC. When stored in sealed glass containers and protected from light, the dose formulations were stable for at least 28 days between –20° C and room temperature. When exposed to air and light, the stability of lauric acid diethanolamine condensate was confirmed for

3 hours; however, there was a 1% loss of weight, and it was recommended that precautions be taken to reduce evaporation of the ethanol.

Periodic analyses of the dose formulations of lauric acid diethanolamine condensate were conducted at the study laboratory using HPLC. For the 14-week studies, dose preparations from the beginning, middle, and end of the studies were analyzed (Table I2). During the 2-year studies, dose preparations were analyzed approximately every 2 months (Table I3). During the 14-week studies, 60% (9/15) of the dose formulations for rats and 67% (10/15) for mice were within 10% of the target concentration; one rat dose formulation from the initial analysis and all rat and mouse dose formulations from the second analysis were more than 10% less than the target concentrations. The one rat dose formulation from the initial analysis was remixed. The dose formulations from the second analysis data were remixed using a freshly opened bottle of lauric acid diethanolamine condensate; all remixes were within 10% of the target concentrations. Throughout the 2-year studies, a fresh bottle of lauric acid diethanolamine condensate was used for each set of dose formulations. All dose formulations analyzed during the 2-year studies were within 10% of the target concentration. In addition to dose formulation analysis prior to dosing, samples collected after dosing (animal room samples) were analyzed periodically. All animal room samples from formulations analyzed during the 14-week studies were within 10% of target concentration. For the 2-year studies, 94% (15/16) were within 10% of the target concentrations. One sample was 126% of target concentration; this was attributed to evaporation of the 95% ethanol vehicle.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to lauric 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 4 weeks old. Animals were quarantined for 14 (rats) or 16 days (mice) and were 7 weeks old on the first day of the studies. Before initiation of the studies, 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 core study rats and 10 male and 10 female clinical pathology rats received dermal applications of 0, 25, 50, 100, 200, or 400 mg lauric acid diethanolamine condensate per kg body weight in ethanol (0, 30, 61, 121, 243, or 485 mg/mL ethanol). Groups of 10 male and 10 female mice received dermal applications of 0, 50, 100, 200, 400, or 800 mg lauric acid diethanolamine condensate per kg body weight in ethanol (0, 20, 40, 80, 160, or 320 mg/mL ethanol). Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded daily, and 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.

Following 4 and 24 days of dosing, blood was collected from the retroorbital sinus of clinical pathology male and female rats from each group for hematology and clinical chemistry analyses. At the end of the 14-week studies, blood was collected from the retroorbital sinus of all core study rats for hematology and clinical chemistry analyses. At all time points, animals were anesthetized with a carbon dioxide/oxygen mixture. Blood for hematology was collected into tubes containing potassium EDTA and gently inverted on an aliquot mixer to prevent clotting. Blood for clinical chemistry was collected into serum separator tubes and allowed to clot, and the serum was obtained by centrifugation. Hematology determinations including erythrocyte and leukocyte counts, hemoglobin concentration, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were performed on the Serono-Baker System 9000 Hematology Analyzer (Serono-Baker Diagnostics, Allentown, PA). Leukocyte differential and nucleated erythrocyte counts and blood cell morphology were determined by microscopic examination of blood films stained with modified Wright-Giemsa. Blood smears prepared from whole blood stained with new methylene blue were examined microscopically for the quantitative determination of reticulocytes. Clinical chemistry analyses were performed on a Hitachi 704 chemistry analyzer (Boehringer Mannheim, Indianapolis, IN)

using commercially available reagents. The parameters measured are listed in Table 1.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on vehicle control animals, rats exposed to 100, 200, or 400 mg/kg, and mice exposed to 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.

Necropsy was performed on all core study rats and 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 core study rats and on vehicle control and 800 mg/kg mice. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats received dermal applications of 0, 50, or 100 mg lauric acid diethanolamine condensate per kg body weight in ethanol (0, 85, or 170 mg/mL ethanol). Groups of 50 male and 50 female mice received dermal applications of 0, 100, or 200 mg lauric acid diethanolamine condensate per kg body weight in ethanol (0, 50, or 100 mg/mL ethanol).

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. 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 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 at the beginning of the study, at 4-week intervals thereafter, and at the end of the study. Body weights were recorded at the beginning of the study, weekly for the first 13 weeks, at 4-week intervals thereafter, and at the end of the study.

Complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trim-

med, 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 kidney (female rats and mice), liver (mice), mammary gland (rats), pancreatic islets (mice), clitoral gland or preputial gland (rats), site of application (all animals), and thyroid gland follicle (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 Lauric Acid Diethanolamine Condensate

	14-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 Farms (Germantown, NY)
Time Held Before Studies	Rats: 14 days Mice: 16 days	Rats: 11 days (males) or 12 days (females) Mice: 13 days (males) or 14 days (females)
Average Age When Studies Began	7 weeks	6 weeks
Date of First Dose	Rats: 13 January 1992 (males) 14 January 1992 (females) Mice: 15 January 1992 (males) 16 January 1992 (females)	Rats: 14 December 1992 (males) 15 December 1992 (females) Mice: 30 December 1992 (males) 31 December 1992 (females)
Duration of Dosing	5 exposures per week for 14 weeks	5 exposures per week for 104-105 weeks (rats) or 105-106 weeks (mice)
Date of Last Dose	Rats: 4 February 1992 (clinical pathology males) 5 February 1992 (clinical pathology females) 13 April 1992 (core study males) 14 April 1992 (core study females) Mice: 15 April 1992 (males) 16 April 1992 (females)	Rats: 13 December 1994 Mice: 5 January 1995
Necropsy Dates	Rats: 14 April 1992 (males) 15 April 1992 (females) Mice: 16 April 1992 (males) 17 April 1992 (females)	Rats: 12-14 December 1994 Mice: 3-6 January 1995
Average Age at Necropsy	20 weeks	110 weeks (rats) 112 weeks (mice)
Size of Study Groups	10 males and 10 females	50 males and 50 females
Method of Distribution	Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-week studies

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

14-Week Studies	2-Year 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* and changed weekly	Same as 14-week studies
Water Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum* and cleaned every 2 weeks	Same as 14-week studies
Cages Polycarbonate (Lab Products, Inc., Maywood, NJ), changed weekly and rotated every 2 weeks	Same as 14-week studies
Bedding Sani-Chip® heat-treated hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed weekly	Same as 14-week studies
Cage Filters Spun-bonded polyester Du Pont 2024 (Snow Filtration, Co., Cincinnati, OH), changed every 2 weeks	Same as 14-week studies
Racks Stainless steel drawer-type (Lab Products, Inc., Maywood, NJ), changed and rotated every 2 weeks	Same as 14-week studies
Animal Room Environment Temperature: 21.6°-23.3° C (rats) 21.1°-23.9° C (mice) Relative humidity: 42%-54% (rats) 42%-57% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 21.1°-26.7° C (rats) 20.5°-26.1° C (mice) Relative humidity: 36%-59% (rats) 33%-64% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour
Dose Levels, Concentrations, and Volume Rats: 0, 25, 50, 100, 200, or 400 mg/kg (0, 30, 61, 121, 243, or 485 mg/mL) in ethanol applied to shaved skin. Dose volumes were calculated by group based on most recent group mean body weight. Mice: 0, 50, 100, 200, 400, or 800 mg/kg (0, 20, 40, 80, 160, or 320 mg/mL) in ethanol applied to shaved skin. Dose volumes were calculated by group based on most recent group mean body weight.	Rats: 0, 50, or 100 mg/kg (0, 85, or 170 mg/mL) in ethanol applied to shaved skin. Dose volumes were calculated by group based on most recent group mean body weight. Mice: 0, 100, or 200 mg/kg (0, 50, or 100 mg/mL) in ethanol applied to shaved skin. Dose volumes were calculated by group based on most recent group mean body weight.
Type and Frequency of Observation Observed twice daily; animal weights and clinical findings were recorded weekly.	Observed twice daily; animals were weighed initially, weekly during weeks 1-13, at 4-week intervals thereafter, and at the end of the studies; clinical findings were recorded initially, at 4-week intervals during the study, and at necropsy.

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

14-Week Studies	2-Year Studies
Method of Sacrifice	
Carbon dioxide asphyxiation	Same as 14-week studies
Necropsy	
Necropsy performed on all core study rats and mice. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals.
Clinical Pathology	
Blood for hematology/clinical chemistry was collected from the retroorbital sinus of anesthetized clinical pathology rats on days 4 and 24 of the dosing and from anesthetized core study rats prior to sacrifice. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differential ***Clinical chemistry:*** blood urea nitrogen; creatinine; total protein; albumin; alanine aminotransferase; alkaline phosphatase; sorbitol dehydrogenase; and total bile acids	None
Histopathology	
Complete histopathology was performed on 0 and 400 mg/kg core study rats and 0 and 800 mg/kg mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, 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 (and epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the skin was examined in all rats and mice.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, 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, spleen, stomach (forestomach and glandular), testis (and epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Motility and Vaginal Cytology	
At the end of the studies, samples were collected for sperm motility or vaginal cytology from all rats in the 0, 100, 200, and 400 mg/kg groups and mice in the 0, 200, 400, and 800 mg/kg groups for evaluations. The following sperm motility parameters were evaluated: spermatid heads per gram of testis, spermatid heads per testis, spermatid count, motility, and concentration in cauda epididymis. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for 12 consecutive days prior to the end of the studies for vaginal cytology evaluations. The length of the estrous cycle and the length of time spent in each stage of the cycle were evaluated.	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 D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

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

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1-P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

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.

Historical Control Data

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

QUALITY ASSURANCE METHODS

The 14-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 lauric acid diethanolamine condensate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in peripheral blood of mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of lauric 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.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the

Salmonella test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

RATS

14-WEEK STUDY

All animals survived to the end of the study. Final mean body weights and body weight gains of males administered 200 or 400 mg/kg were significantly less than those of the vehicle control group (Table 2). The primary clinical finding was irritation of the skin at the site of application in males administered 100 mg/kg or greater and in females administered 200 or 400 mg/kg.

Segmented neutrophil counts were significantly increased on days 4 and 24 and at week 14 in males administered 400 mg/kg and at week 14 in females administered 400 mg/kg (Table F1). At week 14, alkaline phosphatase activity was minimally increased in 400 mg/kg males.

The kidney weights of females administered 200 or 400 mg/kg were significantly greater than those of the vehicle control group (Table G1). In males administered 400 mg/kg, the absolute liver weight was significantly less than that of the vehicle control group; this difference may be related to significantly lower mean body weights in this group of males. There were no significant differences in reproductive tissue evaluations or in estrous cycle characterization between dosed and vehicle control groups (Tables H1 and H2).

TABLE 2
Survival and Body Weights of Rats in the 14-Week Dermal Study of Lauric 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	168 ± 4	366 ± 7	198 ± 5	
25	10/10	168 ± 4	363 ± 5	195 ± 6	99
50	10/10	170 ± 4	364 ± 5	194 ± 4	99
100	10/10	167 ± 3	357 ± 5	190 ± 5	98
200	10/10	167 ± 4	332 ± 4**	164 ± 3**	91
400	10/10	168 ± 4	317 ± 5**	149 ± 4**	87
Female					
0	10/10	126 ± 4	188 ± 5	62 ± 3	
25	10/10	126 ± 3	191 ± 4	64 ± 2	101
50	10/10	126 ± 3	193 ± 2	67 ± 3	103
100	10/10	125 ± 2	186 ± 3	61 ± 4	99
200	10/10	127 ± 3	191 ± 3	64 ± 2	101
400	10/10	127 ± 3	185 ± 4	59 ± 3	99

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Incidences of nonneoplastic lesions of the skin at the site of application significantly increased with increasing dose in males and females (Table 3). These lesions included hyperplasia of the epidermis and sebaceous gland, chronic inflammation, parakeratosis, and ulceration.

Dose Selection Rationale: Dose selection for the 2-year study was based primarily on the increased incidences of a spectrum of skin lesions at the site of application. Doses of 200 and 400 mg/kg caused high incidences of chronic inflammation and ulceration in males and females. Final mean body weights and body weight gains of male rats treated with 200 or 400 mg/kg were also less than those of the vehicle controls. Therefore, 200 and 400 mg/kg were considered inappropriate for a 2-year study. There was a very obvious reduction in toxic response of the skin at 100 mg/kg, with chronic inflammation and ulceration being absent in females and present in only one male; thus, 100 mg/kg was selected as the high dose for the 2-year rat study. The responses observed at 25 and 50 mg/kg were very similar and consisted of only minimal hyperplasia; therefore, 50 mg/kg was selected as the low dose for the 2-year rat study.

TABLE 3
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 14-Week Dermal Study of Lauric 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
Epidermis, Hyperplasia[a]	0	2	8**	10**	10**	10**
Sebaceous Gland, Hyperplasia	0	0	8**	10**	10**	10**
Inflammation, Chronic	0	0	0	1	10**	10**
Parakeratosis	0	0	0	2	10**	10**
Ulcer	0	0	0	1	10**	10**
Female						
Number Examined Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia	0	6**	7**	9**	10**	10**
Sebaceous Gland, Hyperplasia	0	0	7**	8**	9**	10**
Hyperkeratosis	0	0	0	1	2	0
Inflammation, Chronic	0	0	0	0	9**	10**
Parakeratosis	0	0	0	0	7**	10**
Ulcer	0	0	0	0	5*	10**

* 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

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). There were no significant differences in survival between the dosed groups and the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of dosed rats were similar to those of the vehicle control groups throughout the study (Figure 2; Tables 5 and 6). There were no clinical findings attributed to lauric acid diethanolamine condensate administration.

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

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Animals initially in study	50	50	50
Accidental death[a]	0	0	1
Moribund	31	29	25
Natural deaths	7	3	8
Animals surviving to study termination	12	18	16
Percent probability of survival at end of study[b]	24	36	33
Mean survival (days)[c]	657	650	648
Survival analysis[d]	P=0.413N	P=0.614N	P=0.405N
Female			
Animals initially in study	50	50	50
Accidental deaths[a]	1	0	1
Moribund	10	12	5
Natural deaths	11	12	22
Animals surviving to study termination	28	26	22
Percent probability of survival at end of study	57	52	45
Mean survival (days)	653	656	626
Survival analysis	P=0.274	P=0.734	P=0.301

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

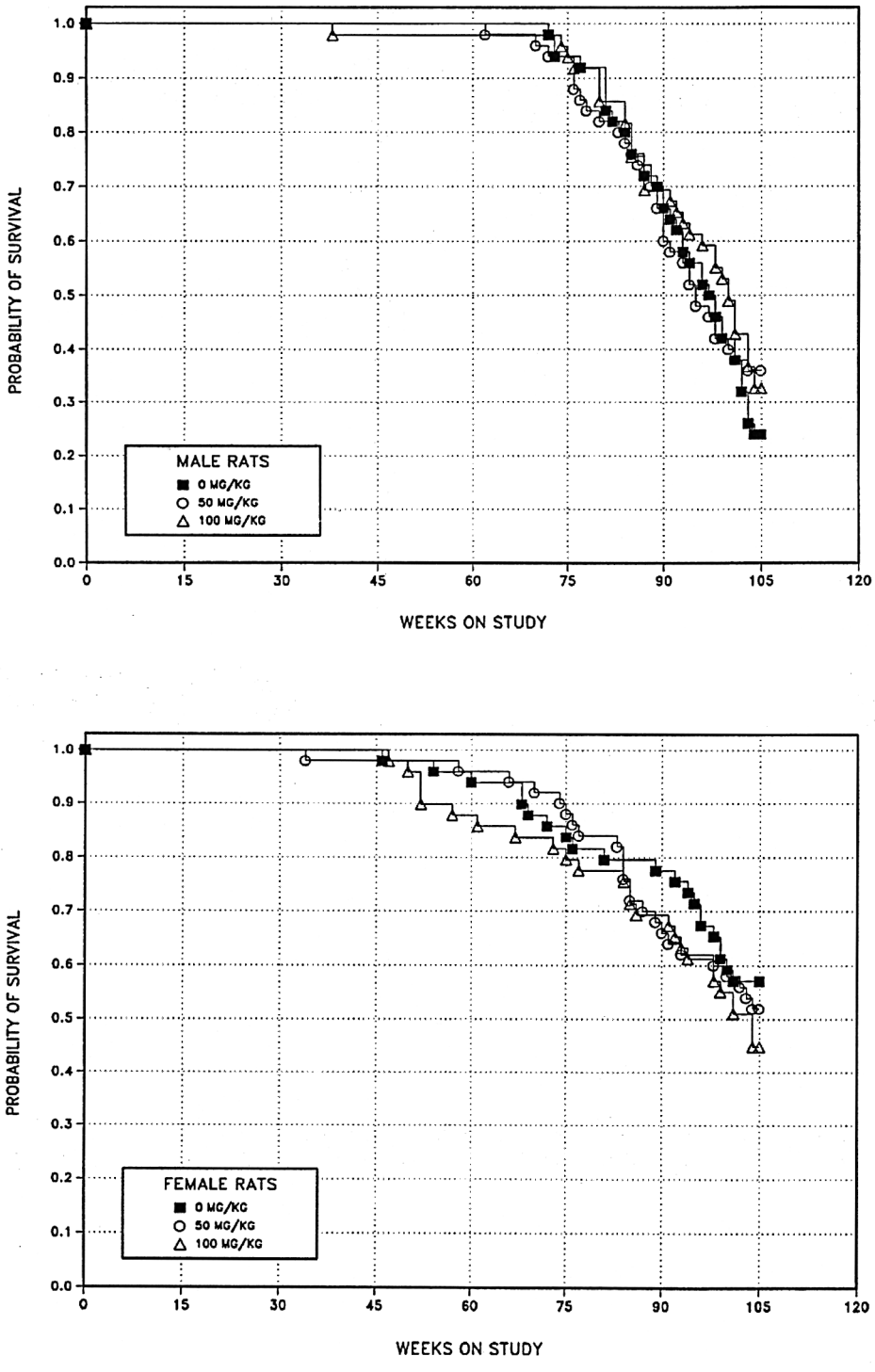


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Lauric Acid Diethanolamine Condensate Dermally for 2 Years

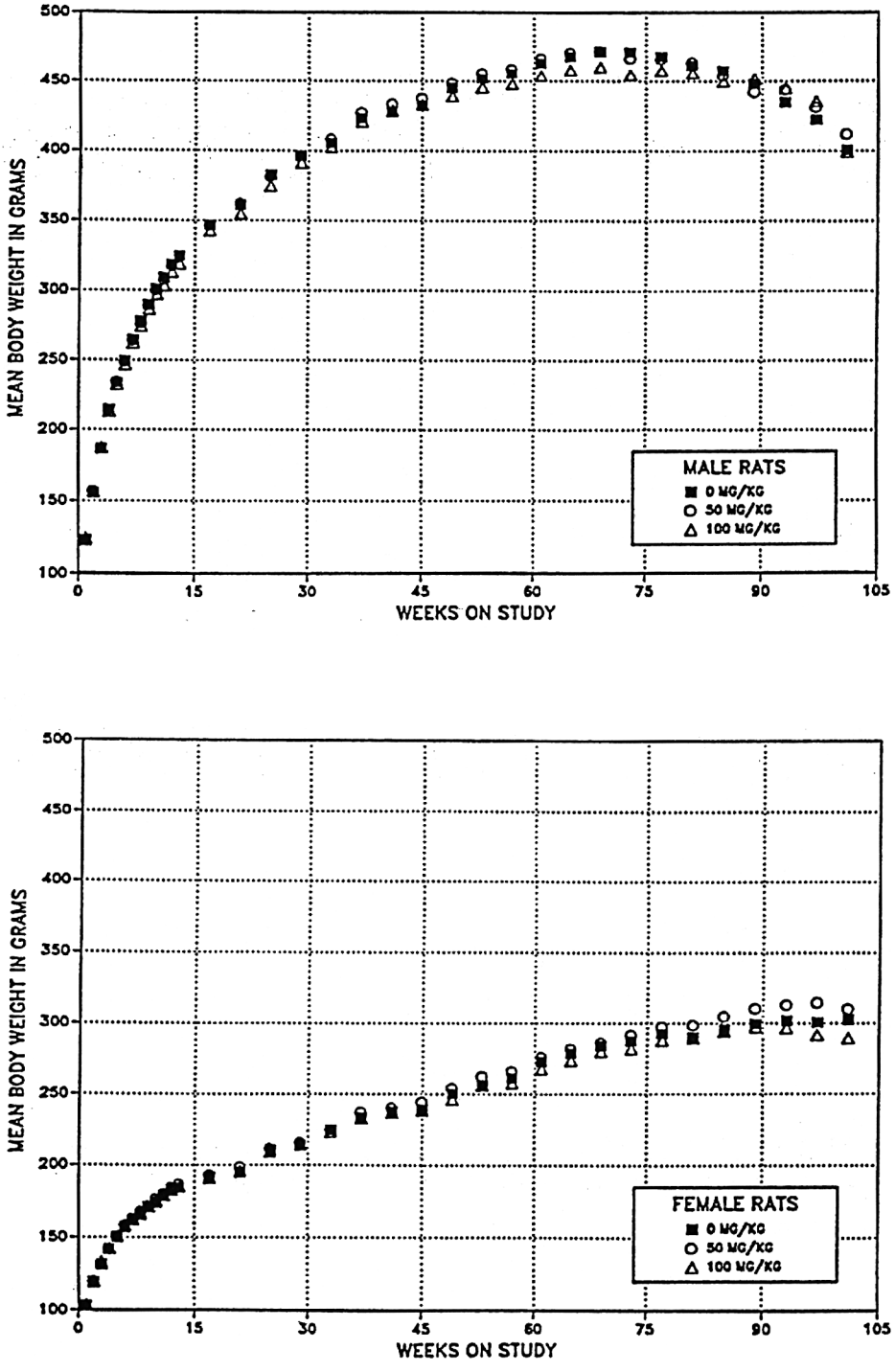


FIGURE 2
Growth Curves for Male and Female Rats Administered Lauric Acid Diethanolamine Condensate Dermally for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Lauric 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	123	50	123	100	50	125	102	50
2	155	50	157	101	50	156	101	50
3	186	50	187	100	50	187	101	50
4	214	50	214	100	50	213	99	50
5	234	50	234	100	50	233	100	50
6	249	50	249	100	50	247	99	50
7	264	50	264	100	50	262	99	50
8	277	50	276	100	50	274	99	50
9	289	50	289	100	50	286	99	50
10	300	50	300	100	50	297	99	50
11	309	50	307	100	50	303	98	50
12	318	50	317	100	50	313	99	50
13	324	50	323	100	50	319	98	50
17	346	50	346	100	50	343	99	49
21	361	50	362	100	50	355	98	49
25	382	50	381	100	50	375	98	49
29	396	50	397	100	50	391	99	49
33	405	50	408	101	50	403	99	49
37	424	50	427	101	50	421	99	49
41	428	50	433	101	50	429	100	48
45	432	50	438	101	50	433	100	48
49	445	50	449	101	50	439	99	48
53	452	50	456	101	50	446	99	48
57	456	50	459	101	50	448	98	48
61	463	50	467	101	50	454	98	48
65	469	50	471	101	49	458	98	48
69	472	50	472	100	49	461	98	48
73	471	49	467	99	47	455	97	48
77	468	47	467	100	44	458	98	45
81	462	46	464	101	41	456	99	42
85	458	40	454	99	39	450	98	40
89	448	36	442	99	35	452	101	34
93	435	31	444	102	29	445	102	32
97	422	26	431	102	24	435	103	29
101	400	21	412	103	20	399	100	24
Mean for weeks								
1-13	249		249	100		247	99	
14-52	402		405	101		399	99	
53-101	452		454	100		447	99	

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Lauric 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	103	50	103	100	50	104	101	50
2	119	50	120	101	50	120	101	50
3	132	50	132	100	50	133	101	50
4	142	50	142	100	50	143	101	50
5	150	50	151	100	50	151	101	50
6	157	50	158	101	50	158	101	50
7	161	50	163	101	50	162	101	49
8	165	50	168	101	50	167	101	49
9	171	50	172	101	50	171	100	49
10	174	50	176	101	50	175	101	49
11	179	50	180	101	50	179	100	49
12	182	50	184	101	50	182	100	49
13	184	50	186	101	50	185	101	49
17	191	50	193	101	50	191	100	49
21	195	50	199	102	50	196	101	49
25	211	50	212	101	50	209	99	49
29	214	50	216	101	50	215	100	49
33	225	49	225	100	50	224	100	49
37	233	49	237	102	49	233	100	49
41	237	49	240	101	49	237	100	49
45	239	49	244	102	49	238	100	49
49	250	48	254	102	49	246	98	48
53	256	48	262	102	49	256	100	44
57	261	47	266	102	49	258	99	44
61	273	46	276	101	48	268	98	43
65	279	46	282	101	48	274	98	42
69	284	44	286	101	47	280	99	41
73	287	42	292	102	46	282	98	41
77	292	40	297	102	43	288	99	39
81	290	40	299	103	42	290	100	38
85	295	39	305	103	38	294	100	37
89	300	38	310	104	35	297	99	34
93	302	37	313	104	32	297	98	32
97	300	33	314	105	31	292	97	30
101	302	29	310	103	29	289	96	27
Mean for weeks								
1-13	155		157	101		156	101	
14-52	222		224	101		221	100	
53-101	286		293	102		282	99	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the skin (site of application) and other organs. 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.

There were no significant differences between the vehicle control groups and dosed groups in the incidences of neoplasms.

Skin, Site of Application: Changes of minimal to moderate severity occurred in the skin at the site of application in treated male and female rats (Table 7). The major alterations from normal skin were thickening of the epidermis (epidermal hyperplasia) and sebaceous gland hyperplasia (which usually occurred along with epidermal hyperplasia). Incidences of chronic inflammation, hyperkeratosis, and parakeratosis in all dosed groups were significantly greater than those in the vehicle controls, as were the incidences of ulceration in 100 mg/kg males and females. One male rat in the 100 mg/kg group had a basal cell carcinoma at the site of application. However, the nonneoplastic skin lesions at the site of application were considered to be indicative of local irritation with no neoplastic or preneoplastic changes.

Other Organs: The incidence of forestomach ulcer was significantly lower in males that received 100 mg/kg than in the vehicle controls (vehicle control, 11/50; 50 mg/kg, 5/50; 100 mg/kg, 3/50; Table A4). The incidences of inflammation of the nasal mucosa were significantly lower in dosed males than in the vehicle controls (11/50, 5/50, 3/50). The incidence of chronic inflammation of the liver was significantly lower in females administered 100 mg/kg than in the vehicle controls (13/50, 15/50, 4/50; Table B4).

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

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Number Examined Microscopically	50	50	50
Epidermis, Hyperplasia[a]	0	29** (1.2)[b]	44** (1.7)
Sebaceous Gland, Hyperplasia	0	27** (1.1)	44** (1.7)
Hyperkeratosis	0	23** (1.4)	25** (1.2)
Inflammation, Chronic	0	10** (1.1)	28** (1.5)
Parakeratosis	0	21** (1.3)	33** (1.9)
Ulcer	0	4 (1.3)	25** (1.9)
Female			
Number Examined Microscopically	50	50	50
Epidermis, Hyperplasia	5 (1.4)	33** (1.2)	44** (1.6)
Sebaceous Gland, Hyperplasia	3 (2.0)	41** (1.1)	45** (1.6)
Hyperkeratosis	0	20** (1.2)	29** (1.3)
Inflammation, Chronic	3 (1.7)	35** (1.0)	34** (1.1)
Parakeratosis	2 (1.5)	12** (1.2)	25** (1.5)
Ulcer	3 (2.0)	2 (1.5)	10* (1.6)

* 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

MICE

14-WEEK STUDY

All mice survived until the end of the study (Table 8). Final mean body weights and body weight gains of dosed males and females were generally similar to those of the vehicle control groups. The primary clinical finding was irritation of the skin at the site of application, which was noted in all males and females administered 400 or 800 mg/kg.

In males, the absolute kidney weights of the 100, 400, and 800 mg/kg groups were significantly greater than that of the vehicle controls, as were the relative kidney weights of all groups of dosed males (Table G2). In females, the absolute and relative kidney weights of the 800 mg/kg group were significantly greater than those of the vehicle controls. The liver weights of the 200, 400, and 800 mg/kg female groups were significantly greater than those of the vehicle control group. The absolute thymus weights of males that received 400 or 800 mg/kg were significantly less than that of the vehicle controls. There were no significant differences between dosed and vehicle control groups in male reproductive tissue evaluations or in estrous cycle characterization (Tables H3 and H4).

Increased incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, chronic inflammation, parakeratosis, and ulcer, were observed in males and females administered 200 mg/kg or greater (Table 9).

TABLE 8
Survival and Body Weights of Mice in the 14-Week Dermal Study of Lauric 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	25.3 ± 0.2	35.4 ± 0.8	10.1 ± 0.7	
50	10/10	25.2 ± 0.3	34.3 ± 0.3	9.0 ± 0.3	97
100	10/10	25.4 ± 0.3	35.2 ± 0.6	9.8 ± 0.6	99
200	10/10	25.2 ± 0.2	33.3 ± 0.7	8.2 ± 0.6*	94
400	10/10	25.7 ± 0.2	34.6 ± 0.5	8.9 ± 0.5	98
800	10/10	25.5 ± 0.2	34.1 ± 0.5	8.6 ± 0.4	96
Female					
0	10/10	20.7 ± 0.2	30.4 ± 0.8	9.7 ± 0.7	
50	10/10	20.7 ± 0.3	30.0 ± 0.5	9.3 ± 0.4	99
100	10/10	20.6 ± 0.3	30.5 ± 0.8	9.9 ± 0.8	100
200	10/10	20.4 ± 0.2	30.7 ± 0.9	10.3 ± 0.8	101
400	10/10	20.6 ± 0.3	29.9 ± 0.4	9.3 ± 0.5	98
800	10/10	20.9 ± 0.3	30.1 ± 0.8	9.3 ± 0.6	99

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

TABLE 9
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 14-Week Dermal Study of Lauric 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
Epidermis, Hyperplasia[a]	0	0	0	6**	9**	10**
Sebaceous Gland, Hyperplasia	0	0	0	8**	9**	10**
Inflammation, Chronic	0	0	0	2	9**	10**
Parakeratosis	0	0	0	1	8**	10**
Ulcer	0	0	0	0	5*	10**
Female						
Number Examined Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia	0	0	2	8**	10**	10**
Sebaceous Gland, Hyperplasia	0	0	2	9**	10**	10**
Inflammation, Chronic	0	0	0	9**	10**	10**
Parakeratosis	0	0	0	1	8**	10**
Ulcer	0	0	0	0	7**	8**

* 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

Dose Selection Rationale: Dose selection for the 2-year study was based primarily on the increased incidences of a spectrum of skin lesions at the site of application. Doses of 400 or 800 mg/kg were associated with high incidences of chronic inflammation and ulceration and were thus considered to be inappropriate for a 2-year study. A marked reduction in toxic response occurred at 200 mg/kg, and 100 mg/kg was a no-effect level in male mice. Therefore, 200 mg/kg was selected as the high dose for the 2-year study and 100 mg/kg was selected as the low dose.

2-YEAR STUDY

Survival

There were no significant differences in survival between dosed males or females and the vehicle control groups (Table 10 and Figure 3).

Body Weights and Clinical Findings

Mean body weights of dosed males and of females that received 100 mg/kg were similar to those of the vehicle control groups (Tables 11 and 12; Figure 4). The mean body weight of females that received 200 mg/kg was 94% that of the vehicle controls by week 33 and remained lower throughout the remainder of the study. There were no clinical findings attributed to lauric acid diethanolamine condensate administration.

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

	Vehicle Control	100 mg/kg	200 mg/kg
Male			
Animals initially in study	50	50	50
Moribund	7	6	7
Natural deaths	3	7	2
Animals surviving to study termination	40	37	41
Percent probability of survival at end of study[a]	80	74	82
Mean survival (days)[b]	700	696	705
Survival analysis[c]	P=0.901N	P=0.684	P=1.000N
Female			
Animals initially in study	50	50	50
Accidental death[d]	0	0	1
Missing[d]	0	1	0
Moribund	9	7	15
Natural deaths	4	2	5
Animals surviving to study termination	37	40	29
Percent probability of survival at end of study	74	82	59
Mean survival (days)	704	707	669
Survival analysis	P=0.109	P=0.445N	P=0.158

[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**.
[d] Censored from survival analyses

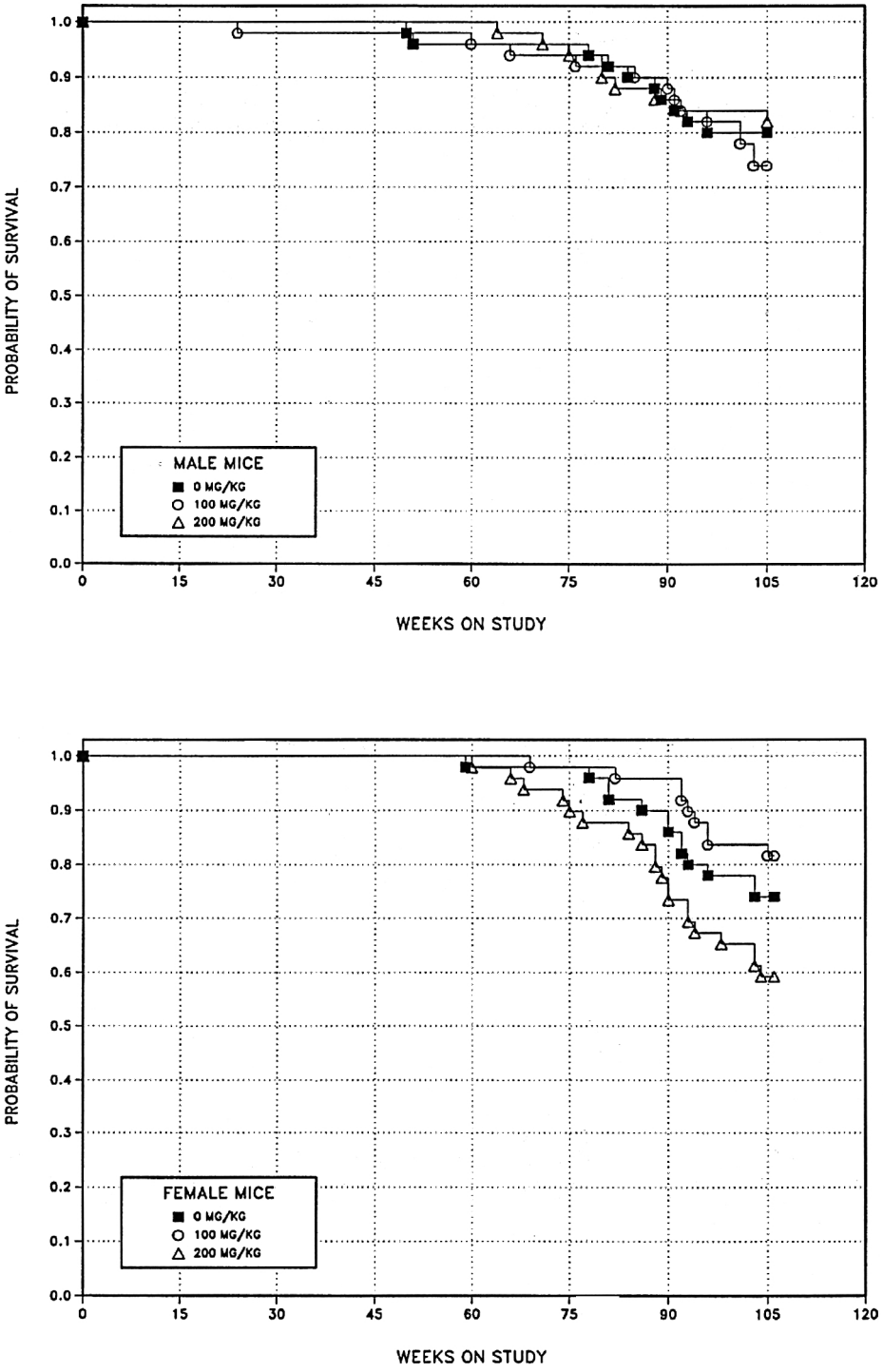


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Mice Administered Lauric Acid Diethanolamine Condensate Dermally for 2 Years

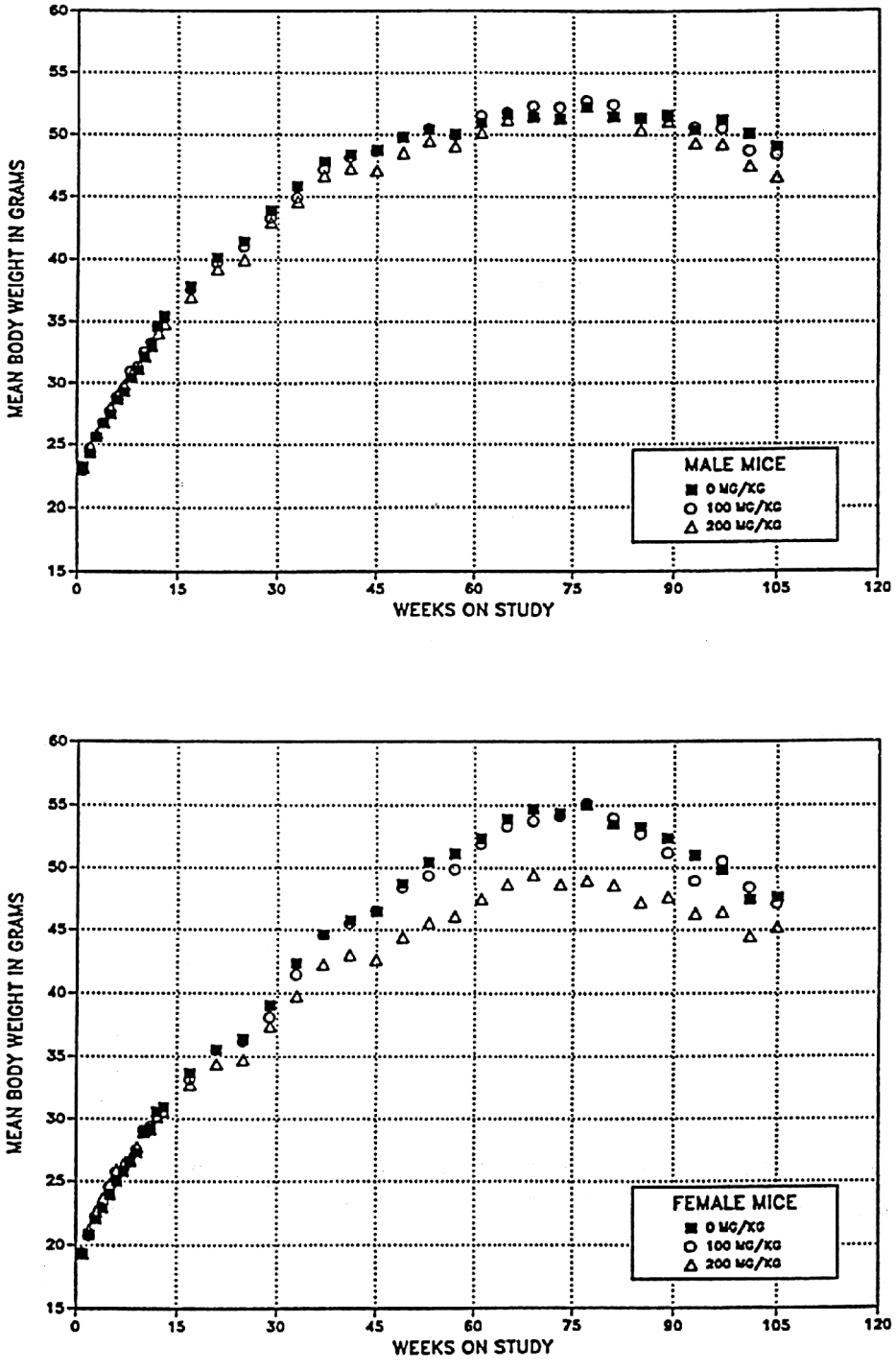


FIGURE 4
Growth Curves for Male and Female Mice Administered Lauric Acid Diethanolamine Condensate Dermally for 2 Years

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

Weeks on Study	Vehicle Control		100 mg/kg			200 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	23.2	50	22.9	99	50	23.1	100	50
2	24.3	50	24.7	102	50	24.8	102	50
3	25.6	50	25.6	100	50	25.9	101	50
4	26.7	50	26.8	100	50	26.8	100	50
5	27.5	50	27.8	101	50	28.0	102	50
6	28.6	50	28.8	101	50	29.0	101	50
7	29.3	50	29.5	101	50	29.8	102	50
8	30.4	50	31.0	102	50	30.8	101	50
9	31.0	50	31.4	101	50	31.2	101	50
10	32.2	50	32.5	101	50	32.2	100	50
11	33.1	50	33.3	101	50	33.0	100	50
12	34.5	50	34.7	101	50	34.1	99	50
13	35.5	50	35.3	99	50	34.8	98	50
17	37.8	50	37.6	100	50	37.0	98	50
21	40.1	50	39.8	99	50	39.2	98	50
25	41.5	50	41.1	99	49	40.0	96	50
29	43.9	50	43.4	99	49	43.0	98	50
33	45.8	50	44.9	98	49	44.7	98	50
37	47.8	50	47.2	99	49	46.7	98	50
41	48.4	50	48.2	100	49	47.3	98	50
45	48.7	50	48.7	100	49	47.1	97	50
49	49.8	50	49.8	100	49	48.5	97	50
53	50.4	48	50.5	100	49	49.5	98	50
57	50.0	48	49.9	100	49	49.1	98	50
61	50.9	48	51.5	101	48	50.2	99	50
65	51.6	48	51.8	100	48	51.2	99	49
69	51.4	48	52.3	102	47	51.7	101	49
73	51.2	48	52.2	102	47	51.3	100	48
77	52.2	48	52.7	101	46	52.2	100	47
81	51.4	47	52.4	102	46	51.6	100	45
85	51.3	45	51.4	100	46	50.4	98	44
89	51.6	44	51.4	100	45	51.1	99	43
93	50.4	42	50.6	100	42	49.4	98	42
97	51.2	40	50.5	99	41	49.3	96	42
101	50.1	40	48.7	97	41	47.6	95	42
105	49.1	40	48.5	99	37	46.7	95	42
Mean for weeks								
1-13	29.4		29.6	101		29.5	100	
14-52	44.9		44.5	99		43.7	97	
53-105	50.9		51.0	100		50.1	98	

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

Weeks on Study	Vehicle Control		100 mg/kg			200 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	19.3	50	19.4	101	50	19.3	100	50
2	20.8	50	20.7	100	50	21.2	102	50
3	22.0	50	22.2	101	50	22.6	103	50
4	22.9	50	23.0	100	50	23.7	104	50
5	23.9	50	24.6	103	50	24.8	104	50
6	25.0	50	25.7	103	50	25.9	104	50
7	25.7	50	25.9	101	50	26.3	102	50
8	26.5	50	26.5	100	50	26.8	101	50
9	27.2	50	27.6	102	50	27.7	102	50
10	28.9	50	29.1	101	50	29.0	100	50
11	29.2	50	29.4	101	50	29.1	100	50
12	30.6	50	30.2	99	50	30.1	98	50
13	30.9	50	30.6	99	50	30.6	99	49
17	33.6	50	33.2	99	50	32.8	98	49
21	35.6	50	35.5	100	50	34.4	97	49
25	36.4	50	36.2	100	50	34.8	96	49
29	39.0	50	38.1	98	50	37.4	96	49
33	42.3	50	41.5	98	49	39.8	94	49
37	44.6	50	44.6	100	49	42.3	95	49
41	45.8	50	45.5	99	49	43.0	94	49
45	46.4	50	46.5	100	49	42.6	92	49
49	48.7	50	48.4	99	49	44.4	91	49
53	50.5	50	49.4	98	49	45.6	90	49
57	51.1	50	49.9	98	49	46.1	90	49
61	52.3	49	51.9	99	49	47.5	91	48
65	53.9	49	53.3	99	49	48.7	90	48
69	54.7	49	53.7	98	49	49.5	91	46
73	54.3	49	54.1	100	48	48.7	90	46
77	55.0	49	55.2	100	48	49.0	89	44
81	53.5	48	53.9	101	48	48.6	91	43
85	53.2	46	52.7	99	47	47.2	89	42
89	52.3	45	51.2	98	47	47.6	91	38
93	51.0	41	49.0	96	45	46.3	91	36
97	49.8	39	50.6	102	41	46.4	93	33
101	47.4	39	48.4	102	41	44.5	94	32
105	47.6	37	47.1	99	41	45.2	95	29
Mean for weeks								
1-13	25.6		25.8	101		25.9	101	
14-52	41.4		41.1	99		39.1	94	
53-105	51.9		51.5	99		47.2	91	

Pathology and Statistical Analyses

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

Liver: The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in dosed female groups compared to that in the vehicle control group, as was the incidence of hepatocellular adenoma in 100 mg/kg females (Table 13). These incidences exceeded the historical control ranges for these neoplasms (Tables 13 and D4). There were also increases in the incidences of eosinophilic foci in dosed female mice, and the increase was significant in females administered 200 mg/kg. The incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) were not significantly increased in dosed male mice (Table C3).

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

	Vehicle Control	100 mg/kg	200 mg/kg
Number Examined Microscopically	50	49	50
Eosinophilic Focus[a]	15	20	23*
Hepatocellular Adenoma			
Overall rate[b]	23/50 (46%)	32/49 (65%)	29/50 (58%)
Adjusted rate[c]	49.5%	68.8%	65.8%
Terminal rate[d]	19/37 (51%)	30/40 (75%)	19/29 (66%)
First incidence (days)	542	651	517
Poly-3 test[e]	P=0.059	P=0.041	P=0.081
Hepatocellular Carcinoma			
Overall rate	10/50 (20%)	13/49 (27%)	16/50 (32%)
Adjusted rate	21.6%	27.9%	38.2%
Terminal rate	6/37 (16%)	10/40 (25%)	11/29 (38%)
First incidence (days)	542	638	615
Poly-3 test	P=0.059	P=0.324	P=0.068
Hepatocellular Adenoma or Carcinoma[f]			
Overall rate	28/50 (56%)	40/49 (82%)	36/50 (72%)
Adjusted rate	59.3%	84.7%	80.3%
Terminal rate	22/37 (60%)	35/40 (88%)	24/29 (83%)
First incidence (days)	542	638	517
Poly-3 test	P=0.009	P=0.004	P=0.019

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
[a] Number of animals with lesion
[b] Number of animals with neoplasm per number of animals with liver examined microscopically
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] 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 the pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[f] Historical incidence for 2-year dermal studies with vehicle control groups (mean ± standard deviation): 149/252 (59.2% ± 6.4%); range, 52%-66%

Skin, Site of Application: Incidences of nonneoplastic lesions of the skin at the site of application were significantly increased in dosed males and females (Table 14). The lesions were of minimal to moderate severity and consisted mostly of thickening of the epidermis (epidermal hyperplasia) and sebaceous gland hyperplasia. These two changes usually occurred simultaneously. Compared to the vehicle controls, the incidences of chronic inflammation and hyperkeratosis were significantly greater in all groups of dosed males and females, and the incidences of parakeratosis were significantly greater in males and females administered 200 mg/kg. Ulcers occurred in a few mice administered 200 mg/kg and were indicative of more severe local irritation. Chronic inflammation consisted of collagenous dermal thickening and was part of the body's chronic response to irritation from the applied compound or to the irritating effects of the dead tissue (ulcer). Hyperkeratosis and parakeratosis are often seen with epidermal hyperplasia; hyperplasia and hyperkeratosis are reactions by the skin to protect against irritants. Parakeratosis (the retention of nuclei in highly keratinized, dead cells), in this case, was probably indicative of rapid cell growth and was considered a minor lesion.

Thyroid Gland: Incidences of focal hyperplasia of thyroid gland follicular cells were increased in dosed male mice; the incidence in the 200 mg/kg group was significantly greater than that in the vehicle control group (vehicle control, 18/50; 100 mg/kg, 24/50; 200 mg/kg, 36/50; Table C4). There were no corresponding increases in the incidences of follicular cell neoplasms.

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

	Vehicle Control	100 mg/kg	200 mg/kg
Male			
Number Examined Microscopically	50	50	50
Epidermis, Hyperplasia[a]	4 (1.0)[b]	45** (1.6)	50** (1.8)
Sebaceous Gland, Hyperplasia	1 (2.0)	45** (1.6)	48** (2.0)
Hyperkeratosis	3 (1.3)	45** (1.5)	49** (1.7)
Inflammation, Chronic	1 (1.0)	13** (1.0)	28** (1.0)
Parakeratosis	0	1 (2.0)	5* (1.6)
Ulcer	0	0	2 (1.5)
Female			
Number Examined Microscopically	50	49	50
Epidermis, Hyperplasia	0	42** (1.6)	50** (2.2)
Sebaceous Gland, Hyperplasia	0	43** (1.7)	45** (2.0)
Hyperkeratosis	4 (1.0)	41** (1.7)	48** (1.9)
Inflammation, Chronic	0	24** (1.0)	40** (1.1)
Parakeratosis	0	3 (1.3)	9** (1.0)
Ulcer	0	0	3 (1.0)

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

GENETIC TOXICOLOGY

Lauric acid diethanolamine condensate (0.3 to 1,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation (Zeiger *et al.*, 1988; Table E1). In addition, no increase in the frequency of mutant colonies of L5178Y mouse lymphoma cells was observed after exposure to lauric acid diethanolamine condensate, with or without S9 (Table E2). In cytogenic tests with cultured Chinese hamster ovary cells, lauric acid diethanolamine condensate was shown to induce sister chromatid exchanges both in the presence and absence of S9 (Loveday *et al.*, 1990; Table E3). However, the number of chromosomal aberrations was not increased in cultured Chinese hamster ovary cells exposed to similar concentrations of lauric acid diethanolamine condensate with or without S9 (Loveday *et al.*, 1990; Table E4). *In vivo*, no increase in the frequency of micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male and female mice treated dermally with lauric acid diethanolamine condensate for 14 weeks (Table E5).

DISCUSSION AND CONCLUSIONS

Lauric 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, lauric acid diethanolamine condensate, oleic 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 contact with the skin. Therefore, this series of studies was conducted by dermal administration.

During the 14-week studies, the most significant toxic response to lauric acid diethanolamine condensate administration occurred in the skin at the site of application. Doses of 200 or 400 mg/kg in rats and 400 or 800 mg/kg in mice produced high incidences of chronic inflammation and ulceration, while only a few occurred at 100 mg/kg in rats and 200 mg/kg in mice. Therefore, doses of 50 and 100 mg/kg were selected for the 2-year rat study, and doses of 100 and 200 mg/kg were selected for the 2-year mouse study.

During the 2-year studies, there was no neoplastic response in the skin of rats or mice associated with lauric acid diethanolamine condensate administration. The increased incidences of ulceration in 100 mg/kg rats was the major difference in response between the 50 and 100 mg/kg rat groups. In the rat study, ulcers were focal, microscopic lesions that were not observable grossly and never progressed to lesions that would compromise the animals or become life threatening. However, the obvious dose response observed in the 50 and 100 mg/kg groups clearly indicated that higher doses would have produced a greater incidence and severity of ulceration. In groups of mice that received 200 mg/kg, there were slight increases in the incidences of ulceration but more substantial increases in the incidences of chronic inflammation compared to groups that received 100 mg/kg. Therefore, it is likely that doses greater than 200 mg/kg would have produced corresponding increases in incidences and severities of ulceration and chronic inflammation and increased the risk of the animals becoming compromised.

The only neoplastic response associated with lauric acid diethanolamine condensate administration occurred in female mice. At the end of the 2-year study, the incidences of hepatocellular adenoma or carcinoma (combined) in the 100 and 200 mg/kg groups of female mice were significantly greater than in the vehicle controls. Mean body weights of 200 mg/kg female mice were reduced from approximately week 33 to the end of the study. No increase in the incidence of neoplasms associated with lauric acid diethanolamine condensate administration occurred in male mice, and mean body weights of all groups of males were similar throughout the study. During the 14-week study, liver weights of female mice were significantly increased in the 200, 400, and 800 mg/kg groups, while liver weights of males were not increased in any dosed group. In male mice, kidney weights were increased in the 100, 400, and 800 mg/kg groups, but the kidney was not a target organ in the 2-year study.

These results 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 incidence of hepatocellular neoplasms in male and female mice and renal tubule neoplasms in male mice. The comparison also reveals a clear gender difference in the response of male and female mice to diethanolamine administration.

The strongest response occurred with diethanolamine (purity greater than 99%) and involved male and female mice (NTP, 1999a). In the diethanolamine study, mice received doses of 0, 40, 80, or 160 mg/kg. In addition to increased incidences of hepatocellular neoplasms, administration of diethanolamine was also associated with significant increases in the multiplicity and size of hepatocellular adenomas and carcinomas in males and females and increased incidences of hepatoblastomas in males. Mean body weights of dosed female mice were depressed more than those of dosed males, and survival of female mice in the 160 mg/kg group was reduced. In addition to the neoplastic response in the liver, increased incidences of renal tubule neoplasms occurred in dosed male mice.

Significant increases in the incidences of hepatocellular neoplasms in mice were also associated with the administration of coconut oil acid diethanolamine condensate (NTP, 1999b); however, there was no corresponding increase in the multiplicity or size of neoplasms as was observed in the diethanolamine study. The incidences of hepatoblastoma were significantly increased in males but not in females. The mean body weight and survival of 200 mg/kg female mice were less than those of the vehicle controls. In male mice, the incidences of renal tubule neoplasms were increased in the 200 mg/kg group and the incidences of thyroid gland follicular cell hyperplasia were increased in the 100 and 200 mg/kg groups. Based on data provided by the manufacturer, coconut oil acid diethanolamine condensate contained 18.2% free diethanolamine by weight; therefore, mice in that study were administered 18.2 or 36.4 mg/kg free diethanolamine.

The weakest positive response occurred in the present study, in which hepatocellular neoplasm incidences were increased only in female mice. Moreover, although the combined incidences of hepatocellular adenoma or carcinoma in dosed female mice were significantly greater than the combined incidence in the vehicle controls, the incidences of hepatocellular adenoma or hepatocellular carcinoma alone were not significantly increased in 200 mg/kg female mice, survival of females was similar to that of the vehicle controls, and no response was observed in the kidney of dosed male mice. Based on data provided by the manufacturer, lauric acid diethanolamine condensate contained 0.83% free diethanolamine by weight; therefore, mice in this study were administered 0.83 or 1.66 mg/kg free diethanolamine.

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

The incidences of thyroid gland follicular cell hyperplasia were increased in dosed male mice in the present study. Similarly increased incidences occurred in male and female mice in the diethanolamine and coconut oil acid diethanolamine condensate studies; no increase in the incidences of thyroid gland follicular cell hyperplasia occurred in dosed male or female mice in the oleic acid diethanolamine condensate study. Therefore, increased incidences of thyroid gland follicular cell hyperplasia also appear to be associated with administration of diethanolamine.

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

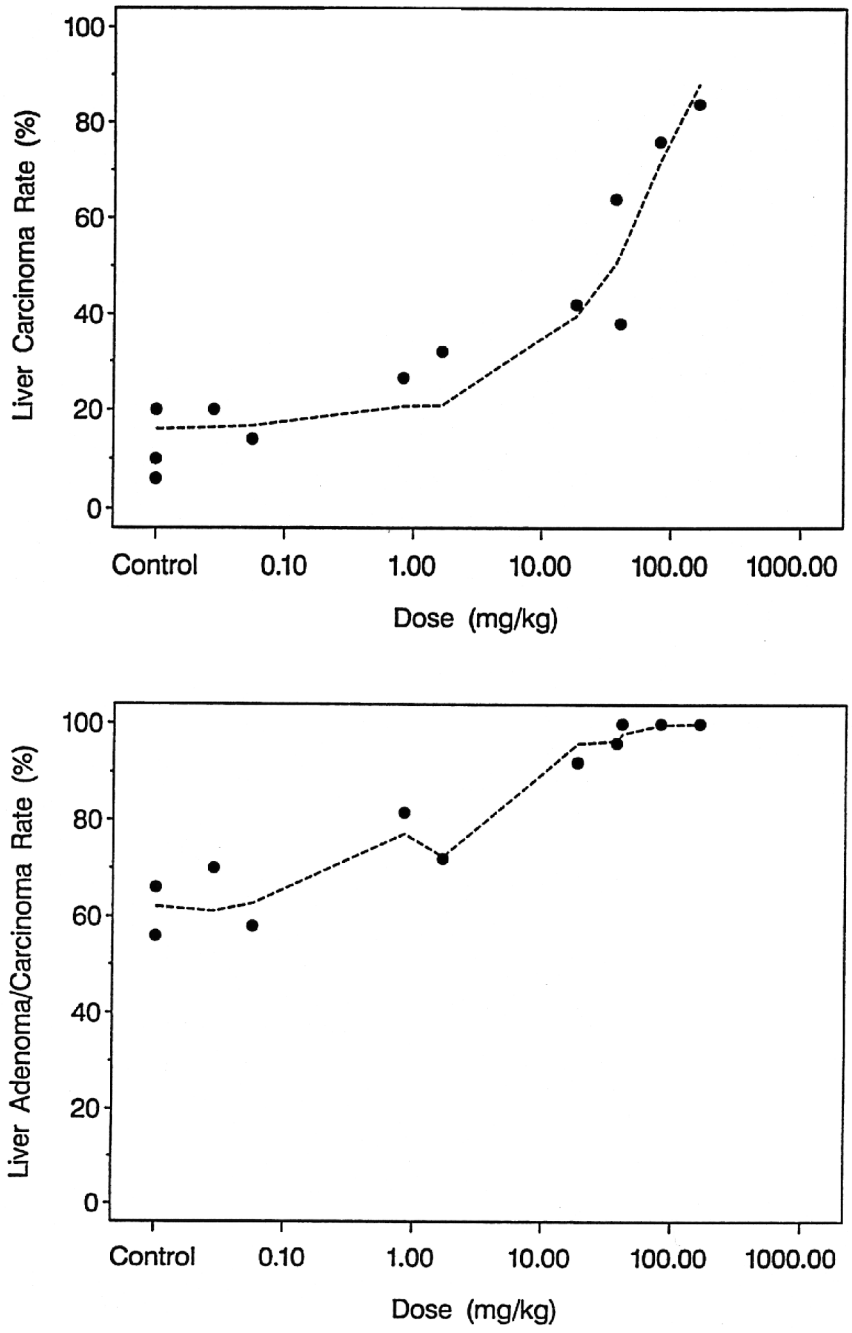


FIGURE 5
Observed and Predicted Liver Neoplasm Incidences in Female B6C3F$_1$ Mice as a Function of Dose and Survival (• = Observed; ----- = Predicted). Predicted rates are based on the logistic regression model P = 1/[1+exp(T)], where P is the probability of observing a neoplasm. For carcinoma, T = 3.2425 – 0.2920D – 0.00226S; and for adenoma/carcinoma, T = 6.3920 – 0.6822D – 0.00979S, where D = dose $^{1/2}$ in mg diethanolamine/kg body weight and S = survival in days.

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.

The composition and purity of the bulk diethanolamide preparations used in these studies varied considerably. Lauric acid diethanolamine condensate was approximately 90% lauric acid diethanolamine, 0.83% free diethanolamine, and 9.17% other organic impurities. Oleic acid diethanolamine condensate was 47.5% oleic acid diethanolamide, 0.19% free diethanolamine, approximately 30% other fatty acid alkanolamides, and 22.31% other organic impurities (most probably unreacted fatty acids). Coconut oil itself is a mixture of fatty acids which typically contains as much as 40% lauric acid. This variable composition was reflected in the composition of coconut oil acid diethanolamine condensate, in which lauric acid diethanolamine condensate was the major constituent. With animals exposed to preparations of such widely varying diethanolamide composition, it seems improbable that the strong correlation between liver neoplasm response and diethanolamine content could have occurred by chance or that the response that occurred in the diethanolamide studies would involve the same species, gender, and target tissues as observed in the diethanolamine studies. Therefore, the increased incidences of hepatocellular neoplasms in this dermal study appear to be strongly associated with the presence of free diethanolamine.

Absorption, distribution, and metabolism studies reveal that lauric acid diethanolamine condensate is well absorbed after dermal or oral administration and is eliminated primarily in the urine as the half amides of succinic and adipic acid (Mathews *et al.,* 1996). This suggests that lauric acid diethanolamine condensate metabolism involves ω-hydroxylation followed by β-oxidation to half amides that are eliminated in the urine. No parent diethanolamide, diethanolamine, or diethanolamine-derived metabolites were detected in urine even after oral doses of 1,000 mg/kg. Therefore, no additional, bioavailable diethanolamine is released as a result of metabolic cleavage of the amide linkage, specifically for lauric acid diethanolamine condensate, and quite likely for coconut oil and oleic acid diethanolamine condensates as well.

The results of the current study, the diethanolamine study, and the other diethanolamide studies are consistent with an association between the increased incidences of hepatocellular neoplasms in male and female mice and of renal tubule neoplasms in male mice and the presence of free, unreacted diethanolamine.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of lauric acid diethanolamine condensate in male or female F344/N rats administered 50 or 100 mg/kg or in male $B6C3F_1$ mice administered 100 or 200 mg/kg. There was *some evidence of carcinogenic activity* in female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms. These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate.

Dermal administration of lauric acid diethanolamine condensate to rats and mice for 2 years resulted in increased incidences of epidermal and sebaceous gland hyperplasia, hyperkeratosis, chronic inflammation, and parakeratosis at the site of application. Lauric acid diethanolamine condensate administration also resulted in increased incidences of thyroid gland follicular cell hyperplasia in dosed male mice.

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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.

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental death			1
Moribund	31	29	25
Natural deaths	7	3	8
Survivors			
Terminal sacrifice	12	18	16
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(49)	(50)	(46)
Intestine large, cecum	(41)	(47)	(44)
Intestine small, duodenum	(50)	(50)	(50)
Intestine small, jejunum	(45)	(50)	(46)
Adenocarcinoma			1 (2%)
Intestine small, ileum	(45)	(45)	(44)
Liver	(50)	(50)	(50)
Osteosarcoma, metastatic, bone		1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)		
Mesentery	(12)	(8)	(6)
Lipoma			1 (17%)
Oral mucosa		(1)	(1)
Squamous cell papilloma		1 (100%)	1 (100%)
Pancreas	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
Tongue	(1)		
Squamous cell papilloma	1 (100%)		
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Heart	(50)	(50)	(50)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma			1 (2%)
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma malignant	2 (4%)		
Pheochromocytoma benign	2 (4%)	2 (4%)	5 (10%)
Bilateral, pheochromocytoma benign			2 (4%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	4 (8%)
Adenoma, multiple			1 (2%)
Carcinoma	4 (8%)	1 (2%)	2 (4%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	48 (96%)	45 (90%)	44 (88%)
Pars distalis, adenoma, multiple			2 (4%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	2 (4%)	3 (6%)	2 (4%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma		1 (2%)	1 (2%)
Follicular cell, carcinoma			1 (2%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)
Adenoma	4 (8%)		2 (4%)
Carcinoma	2 (4%)	2 (4%)	1 (2%)
Prostate	(50)	(50)	(49)
Seminal vesicle	(50)	(50)	(49)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma	20 (40%)	22 (44%)	17 (34%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)		
Lymph node	(2)	(4)	
Lymph node, mandibular	(50)	(50)	(50)
Sarcoma			1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)
Spleen	(50)	(50)	(50)
Fibroma		1 (2%)	
Thymus	(44)	(50)	(47)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System			
Mammary gland	(50)	(50)	(49)
Carcinoma		1 (2%)	
Fibroadenoma	2 (4%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)
Basal cell adenoma	1 (2%)		
Basal cell carcinoma			1 (2%)
Keratoacanthoma	5 (10%)		2 (4%)
Squamous cell carcinoma	1 (2%)		
Trichoepithelioma	1 (2%)		1 (2%)
Pinna, squamous cell papilloma		1 (2%)	
Sebaceous gland, adenoma			1 (2%)
Sebaceous gland, skin, site of application, basal cell adenoma			1 (2%)
Skin, site of application, squamous cell papilloma		1 (2%)	
Subcutaneous tissue, fibroma	3 (6%)	5 (10%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, lipoma		1 (2%)	
Subcutaneous tissue, myxosarcoma		1 (2%)	
Musculoskeletal System			
Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
Nervous System			
Brain	(50)	(50)	(50)
Meningioma benign	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)
Chordoma, metastatic, uncertain primary site	1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)		
Special Senses System			
Zymbal's gland			(2)
Carcinoma			2 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)		
Leukemia mononuclear	6 (12%)	12 (24%)	8 (16%)
Lymphoma malignant			1 (2%)
Mesothelioma benign			1 (2%)
Mesothelioma malignant	6 (12%)	3 (6%)	1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	50	49	48
Total primary neoplasms	117	109	114
Total animals with benign neoplasms	48	46	48
Total benign neoplasms	92	86	92
Total animals with malignant neoplasms	23	21	19
Total malignant neoplasms	25	23	22
Total animals with metastatic neoplasms	2	1	
Total metastatic neoplasms	4	2	
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 A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: Vehicle Control

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

Number of Days on Study	6 8 0	6 8 4	6 8 9	6 9 1	7 0 2	7 0 3	7 0 8	7 1 0	7 1 0	7 1 5	7 1 5	7 1 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2	0 3 7	0 2 2	0 0 6	0 2 3	0 0 7	0 2 4	0 2 7	0 3 4	0 1 2	0 4 0	0 4 9	1 1 8	1 1 1	1 1 5	1 1 6	1 2 9	1 3 0	1 3 8	1 4 5	1 4 0	1 4 8	1 1 4	1 1 7	1 4 2	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	A	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla													X												1
Mesentery					+		+		+		+									+	+				12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																									1
Tongue																									1
Squamous cell papilloma																									1
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant													X											X	2
Pheochromocytoma benign																									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X								2
Carcinoma											X														4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	X	X	X	X	X	X	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X				X														2
C-cell, carcinoma															X										1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X										4
Carcinoma		X																							2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma					X	X	X		X		X		X		X	X	X	X	X	X	X	X	X		X	20

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

Number of Days on Study	5 0 0	5 0 6	5 0 9	5 3 5	5 6 3	5 6 5	5 6 5	5 6 5	5 6 9	5 8 3	5 8 9	5 8 9	6 0 7	6 0 9	6 1 8	6 2 4	6 2 6	6 3 4	6 4 1	6 4 5	6 4 6	6 5 4	6 6 8	6 7 0	6 7 4
Carcass ID Number	0 2 5	0 3 1	0 0 3	0 0 9	0 2 0	0 1 9	0 3 5	0 5 0	0 3 2	0 3 9	0 4 3	0 4 7	0 4 6	0 2 8	0 4 4	0 3 3	0 1 3	0 1 0	0 4 8	0 4 1	0 3 6	0 2 1	0 2 6	0 0 1	0 0 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Lymph node										+															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma														X	X										
Squamous cell carcinoma																									
Trichoepithelioma																							X		
Subcutaneous tissue, fibroma																					X				
Subcutaneous tissue, fibrosarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, uncertain primary site			X																						
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic																									
Leukemia mononuclear		X								X												X			
Mesothelioma malignant			X						X										X						

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

Number of Days on Study	6 8 0	6 8 4	6 8 9	6 9 1	7 0 2	7 0 3	7 0 8	7 1 0	7 1 0	7 1 5	7 1 5	7 1 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2	0 3 7	0 2 2	0 0 6	0 2 3	0 0 7	0 2 4	0 2 7	0 3 4	0 1 2	0 4 0	0 4 9	0 1 8	0 1 1	0 1 5	0 1 6	0 2 9	0 3 0	0 3 8	0 4 5	0 0 4	0 0 8	0 1 4	0 1 7	0 4 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla													X													1
Lymph node			+																							2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma															X											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																				X						1
Keratoacanthoma						X					X														X	5
Squamous cell carcinoma						X																				1
Trichoepithelioma																										1
Subcutaneous tissue, fibroma						X											X									3
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, uncertain primary site																										1
Pheochromocytoma malignant, metastatic, adrenal medulla													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																						X				1
Leukemia mononuclear					X		X																		X	6
Mesothelioma malignant										X							X		X							6

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

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

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

Number of Days on Study	6 6 3	6 7 4	6 8 0	6 8 4	6 9 6	7 0 5	7 1 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 6 7	0 6 9	0 7 3	0 8 8	0 6 5	0 6 4	0 5 4	0 5 6	0 5 8	0 5 9	0 6 3	0 6 6	0 7 0	0 7 9	0 8 4	0 8 5	0 8 7	0 9 7	0 9 9	0 6 2	0 7 5	0 7 8	0 8 0	0 8 3	0 9 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Mesentery							+	+	+				+							+						8
Oral mucosa								+																		1
Squamous cell papilloma								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X																		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Carcinoma																						X				1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	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	X	X	X	X	X	X	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X														X			X	3
Follicular cell, adenoma																						X				1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									X	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma			X	X			X	X	X	X	X		X	X	X	X	X			X	X	X	X		X	22

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

Number of Days on Study	430	485	500	526	556	627	737	744	757	782	829	896	973	1334	1418	1480	1620	1625	1626	1634	1646	1653	1658	1662
Carcass ID Number	01	05	07	05	05	06	07	08	05	08	09	09	09	07	08	01	09	05	07	09	08	06	09	09	06
	71	57	74	52	55	00	76	22	11	66	22	66	88	77	99	00	11	33	22	33	11	88	55	44	61
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+						+	+				+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, squamous cell papilloma																									
Skin, site of application, squamous cell papilloma																						X			
Subcutaneous tissue, fibroma													X		X				X		X				
Subcutaneous tissue, fibrosarcoma															X										
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, myxosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, bone	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																				+					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X							X			X	X		X	X	X			X	
Mesothelioma malignant					X																				

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

Number of Days on Study	6 6 3	6 7 4	6 8 0	6 8 4	6 9 6	7 0 5	7 1 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 6 7	0 6 9	0 7 3	0 8 8	0 6 5	0 6 4	0 5 4	0 5 6	0 5 8	0 5 9	0 6 3	0 6 6	0 7 0	0 7 9	0 8 4	0 8 5	0 8 7	0 9 7	0 9 9	0 6 2	0 7 5	0 7 8	0 8 0	0 8 3	0 9 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									X	1
Fibroadenoma																								X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, squamous cell papilloma																								X		1
Skin, site of application, squamous cell papilloma																										1
Subcutaneous tissue, fibroma					X																					5
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma														X												1
Subcutaneous tissue, myxosarcoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma					X																					1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X								X		X				X										12
Mesothelioma malignant								X		X																3

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

Number of Days on Study	1060	2066	5134	5227	5275	5557	5578	5583	5833	5899	5899	5899	6033	6033	6065	6322	6422	6455	6540	6570	6683	6884	6899	6995
Carcass ID Number	12040	12044	11413	13434	13636	13303	10401	14044	10402	13232	12101	13737	14343	14466	14047	10526	12202	12303	10808	10909	10404	13808	11919	13010	11016
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, cecum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Adenocarcinoma																									
Intestine small, ileum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																+							+	+	
Lipoma																							X		
Oral mucosa																									
Squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Adenoma, multiple																									
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	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	X	X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
Follicular cell, adenoma																X									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma						X								X		X									

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

Number of Days on Study	6 9 6	7 0 3	7 0 3	7 0 3	7 1 7	7 1 9	7 1 9	7 2 6	7 2 7	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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 1 4	1 2 5	1 2 7	1 3 5	1 2 9	1 0 3	1 0 6	1 4 2	1 1 7	1 1 1	1 1 2	1 1 3	1 1 8	1 2 6	1 2 8	1 3 1	1 4 5	1 4 8	1 4 9	1 0 7	1 1 0	1 1 5	1 3 9	1 4 0	1 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma																							X			1
Intestine small, ileum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery															+			+							+	6
Lipoma																										1
Oral mucosa									+																	1
Squamous cell papilloma									X																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X	X								X			X					5
Bilateral, pheochromocytoma benign																			X				X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X														X				X					4
Adenoma, multiple	X																									1
Carcinoma											X															2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	X	X			X	X	44
Pars distalis, adenoma, multiple																	X						X			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X						2
Follicular cell, adenoma																										1
Follicular cell, carcinoma																				X						1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X				X												2
Carcinoma				X																						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma		X		X			X	X	X	X			X		X	X	X			X	X	X			X	17

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

Number of Days on Study	1060	2066	5133	5222	5277	5555	5577	5588	5583	5833	5899	5899	5899	6033	6036	6056	6322	6422	6455	6540	6700	6883	6884	6891	6995
Carcass ID Number	12020	12044	14101	13414	13636	13033	10101	14044	10202	13232	12101	13707	14343	14406	14047	10505	12202	12303	10808	10909	10404	13838	11919	13030	11016
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma										X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma								X													X				
Trichoepithelioma																									
Sebaceous gland, adenoma																									
Sebaceous gland, skin, site of application, basal cell adenoma																									
Subcutaneous tissue, fibroma															X										
Subcutaneous tissue, fibrosarcoma																				X		X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																					+				
Zymbal's gland					+	+																			
Carcinoma					X	X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X	X	X	X					X			
Lymphoma malignant																									
Mesothelioma benign																									
Mesothelioma malignant																	X								

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

Number of Days on Study	6 9 6	7 0 3	7 0 3	7 0 3	7 1 7	7 1 9	7 1 9	7 2 6	7 2 7	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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 1 4	1 2 5	1 2 7	1 3 5	1 2 9	1 0 3	1 0 6	1 4 2	1 1 7	1 1 1	1 1 2	1 1 3	1 1 8	1 2 6	1 2 8	1 3 1	1 4 5	1 4 8	1 4 9	1 0 7	1 1 0	1 1 5	1 3 9	1 4 0	1 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																	X				X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma		X																								1
Keratoacanthoma																										2
Trichoepithelioma																		X								1
Sebaceous gland, adenoma						X																				1
Sebaceous gland, skin, site of application, basal cell adenoma																					X					1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																							2
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X												X									X				8
Lymphoma malignant																									X	1
Mesothelioma benign			X																							1
Mesothelioma malignant																										1

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rate[b]	5.2%	5.3%	18.2%
Terminal rate[c]	0/12 (0%)	1/18 (6%)	5/16 (31%)
First incidence (days)	641	626	645
Poly-3 test[d]	P=0.038	P=0.686	P=0.074
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	4/50 (8%)	2/50 (4%)	7/50 (14%)
Adjusted rate	10.4%	5.3%	18.2%
Terminal rate	1/12 (8%)	1/18 (6%)	5/16 (31%)
First incidence (days)	641	626	645
Poly-3 test	P=0.180	P=0.348N	P=0.255
Mammary Gland: Fibroadenoma or Carcinoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	5.2%	8.0%	5.3%
Terminal rate	1/12 (8%)	2/18 (11%)	2/16 (13%)
First incidence (days)	565	614	729 (T)
Poly-3 test	P=0.591	P=0.489	P=0.693
Pancreatic Islets: Adenoma			
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted rate	5.2%	2.7%	12.9%
Terminal rate	1/12 (8%)	1/18 (6%)	2/16 (13%)
First incidence (days)	583	729 (T)	603
Poly-3 test	P=0.132	P=0.511N	P=0.218
Pancreatic Islets: Carcinoma			
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	10.2%	2.7%	5.2%
Terminal rate	0/12 (0%)	1/18 (6%)	1/16 (6%)
First incidence (days)	565	729 (T)	683
Poly-3 test	P=0.244N	P=0.194N	P=0.348N
Pancreatic Islets: Adenoma or Carcinoma			
Overall rate	6/50 (12%)	2/50 (4%)	7/50 (14%)
Adjusted rate	15.1%	5.4%	18.0%
Terminal rate	1/12 (8%)	2/18 (11%)	3/16 (19%)
First incidence (days)	565	729 (T)	603
Poly-3 test	P=0.421	P=0.153N	P=0.483
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	48/50 (96%)	45/50 (90%)	46/50 (92%)
Adjusted rate	98.6%	93.6%	96.6%
Terminal rate	12/12 (100%)	17/18 (94%)	15/16 (94%)
First incidence (days)	509	485	513
Poly-3 test	P=0.373N	P=0.174N	P=0.505N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Preputial Gland: Adenoma			
Overall rate	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	10.3%	0.0%	5.3%
Terminal rate	1/12 (8%)	0/18 (0%)	2/16 (13%)
First incidence (days)	589	—[e]	729 (T)
Poly-3 test	P=0.223N	P=0.065N	P=0.345N
Preputial Gland: Adenoma or Carcinoma			
Overall rate	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted rate	15.1%	5.3%	7.9%
Terminal rate	1/12 (8%)	1/18 (6%)	2/16 (13%)
First incidence (days)	500	500	703
Poly-3 test	P=0.177N	P=0.146N	P=0.259N
Skin: Keratoacanthoma			
Overall rate	5/50 (10%)	0/50 (0%)	2/50 (4%)
Adjusted rate	12.9%	0.0%	5.1%
Terminal rate	1/12 (8%)	0/18 (0%)	0/16 (0%)
First incidence (days)	609	—	558
Poly-3 test	P=0.113N	P=0.033N	P=0.212N
Skin: Squamous Cell Papilloma or Keratoacanthoma			
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.9%	5.3%	5.1%
Terminal rate	1/12 (8%)	1/18 (6%)	0/16 (0%)
First incidence (days)	609	646	558
Poly-3 test	P=0.143N	P=0.228N	P=0.212N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma			
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.9%	5.3%	5.1%
Terminal rate	1/12 (8%)	1/18 (6%)	0/16 (0%)
First incidence (days)	609	646	558
Poly-3 test	P=0.143N	P=0.228N	P=0.212N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma			
Overall rate	7/50 (14%)	2/50 (4%)	4/50 (8%)
Adjusted rate	17.9%	5.3%	10.3%
Terminal rate	2/12 (17%)	1/18 (6%)	1/16 (6%)
First incidence (days)	609	646	558
Poly-3 test	P=0.182N	P=0.085N	P=0.257N
Skin (Subcutaneous Tissue): Fibroma			
Overall rate	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted rate	7.8%	12.9%	2.6%
Terminal rate	1/12 (8%)	0/18 (0%)	0/16 (0%)
First incidence (days)	646	597	603
Poly-3 test	P=0.257N	P=0.362	P=0.301N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Myxosarcoma			
Overall rate	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted rate	10.3%	15.5%	7.7%
Terminal rate	1/12 (8%)	0/18 (0%)	0/16 (0%)
First incidence (days)	563	597	603
Poly-3 test	P=0.424N	P=0.368	P=0.497N
Testes: Adenoma			
Overall rate	20/50 (40%)	22/50 (44%)	17/50 (34%)
Adjusted rate	50.5%	56.0%	42.8%
Terminal rate	10/12 (83%)	14/18 (78%)	9/16 (56%)
First incidence (days)	609	597	555
Poly-3 test	P=0.271N	P=0.389	P=0.315N
Thyroid Gland (C-cell): Adenoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	5.3%	8.1%	5.2%
Terminal rate	0/12 (0%)	3/18 (17%)	1/16 (6%)
First incidence (days)	708	729 (T)	645
Poly-3 test	P=0.589N	P=0.489	P=0.691N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	7.9%	8.1%	5.2%
Terminal rate	1/12 (8%)	3/18 (17%)	1/16 (6%)
First incidence (days)	708	729 (T)	645
Poly-3 test	P=0.406N	P=0.654	P=0.495N
All Organs: Mononuclear Cell Leukemia			
Overall rate	6/50 (12%)	12/50 (24%)	8/50 (16%)
Adjusted rate	15.2%	29.6%	20.0%
Terminal rate	1/12 (8%)	3/18 (17%)	2/16 (13%)
First incidence (days)	506	527	603
Poly-3 test	P=0.356	P=0.096	P=0.396
All Organs: Benign or Malignant Mesothelioma			
Overall rate	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	15.2%	8.0%	5.2%
Terminal rate	2/12 (17%)	2/18 (11%)	0/16 (0%)
First incidence (days)	509	526	632
Poly-3 test	P=0.091N	P=0.260N	P=0.136N
All Organs: Benign Neoplasms			
Overall rate	48/50 (96%)	46/50 (92%)	48/50 (96%)
Adjusted rate	98.6%	95.7%	99.9%
Terminal rate	12/12 (100%)	18/18 (100%)	16/16 (100%)
First incidence (days)	509	485	513
Poly-3 test	P=0.466	P=0.357N	P=0.802

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

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Malignant Neoplasms			
Overall rate	23/50 (46%)	21/50 (42%)	19/50 (38%)
Adjusted rate	52.3%	48.7%	45.0%
Terminal rate	5/12 (42%)	6/18 (33%)	7/16 (44%)
First incidence (days)	500	430	527
Poly-3 test	P=0.279N	P=0.447N	P=0.316N
All Organs: Benign or Malignant Neoplasms			
Overall rate	50/50 (100%)	49/50 (98%)	48/50 (96%)
Adjusted rate	100.0%	98.7%	99.9%
Terminal rate	12/12 (100%)	18/18 (100%)	16/16 (100%)
First incidence (days)	500	430	513
Poly-3 test	P=0.803N	P=0.719N	P=1.000N

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental death			1
Moribund	31	29	25
Natural deaths	7	3	8
Survivors			
Terminal sacrifice	12	18	16
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(49)	(50)	(46)
Cyst		1 (2%)	
Parasite metazoan	4 (8%)		
Intestine large, rectum	(48)	(49)	(47)
Parasite metazoan	2 (4%)	2 (4%)	5 (11%)
Intestine large, cecum	(41)	(47)	(44)
Ulcer	1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)
Ulcer	1 (2%)		
Intestine small, jejunum	(45)	(50)	(46)
Inflammation, chronic			1 (2%)
Liver	(50)	(50)	(50)
Eosinophilic focus	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	
Hepatodiaphragmatic nodule	5 (10%)	8 (16%)	6 (12%)
Hypertrophy		1 (2%)	
Inflammation, chronic active	6 (12%)	4 (8%)	3 (6%)
Necrosis	2 (4%)		2 (4%)
Vacuolization cytoplasmic	11 (22%)	14 (28%)	15 (30%)
Bile duct, hyperplasia	7 (14%)	6 (12%)	6 (12%)
Periportal, fibrosis		1 (2%)	
Mesentery	(12)	(8)	(6)
Arteriole, inflammation, chronic active		1 (13%)	
Fat, inflammation, chronic active	12 (100%)	6 (75%)	2 (33%)
Fat, mineralization	6 (50%)	4 (50%)	1 (17%)
Fat, necrosis			1 (17%)
Pancreas	(50)	(50)	(50)
Cyst	1 (2%)		
Inflammation, chronic active		1 (2%)	
Acinus, atrophy	5 (10%)	5 (10%)	11 (22%)
Arteriole, inflammation, chronic active			1 (2%)
Salivary glands	(50)	(50)	(50)
Atrophy			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Edema			2 (4%)
Fibrosis		1 (2%)	
Hyperkeratosis	1 (2%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)	2 (4%)	
Inflammation, chronic active	10 (20%)	6 (12%)	7 (14%)
Mineralization	1 (2%)		
Ulcer	11 (22%)	5 (10%)	3 (6%)

[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 Lauric Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Stomach, glandular	(50)	(50)	(50)
Erosion	1 (2%)		
Mineralization	1 (2%)		3 (6%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Mineralization			2 (4%)
Heart	(50)	(50)	(50)
Mineralization	2 (4%)		2 (4%)
Thrombosis		1 (2%)	1 (2%)
Myocardium, inflammation, chronic active	36 (72%)	39 (78%)	41 (82%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	7 (14%)	6 (12%)
Degeneration		1 (2%)	1 (2%)
Hyperplasia			3 (6%)
Mineralization	1 (2%)		
Pigmentation, lipofuscin	1 (2%)		
Thrombosis	1 (2%)		
Vacuolization cytoplasmic	19 (38%)	21 (42%)	22 (44%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	4 (8%)	2 (4%)	1 (2%)
Mineralization			1 (2%)
Parathyroid gland	(47)	(45)	(47)
Hyperplasia	16 (34%)	17 (38%)	13 (28%)
Pituitary gland	(50)	(50)	(50)
Cyst		1 (2%)	
Hyperplasia		1 (2%)	1 (2%)
Mineralization			1 (2%)
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)		
C-cell, hyperplasia	3 (6%)		3 (6%)
Follicle, cyst	4 (8%)		2 (4%)
General Body System			
None			
Genital System			
Penis		(1)	
Congestion		1 (100%)	
Preputial gland	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	50 (100%)	46 (92%)	43 (86%)
Inflammation, suppurative		1 (2%)	1 (2%)
Prostate	(50)	(50)	(49)
Cyst		1 (2%)	1 (2%)
Fibrosis			1 (2%)
Inflammation, chronic active	7 (14%)	5 (10%)	3 (6%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System (continued)			
Seminal vesicle	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)
Testes	(50)	(50)	(50)
Degeneration	15 (30%)	16 (32%)	17 (34%)
Inflammation, chronic active	2 (4%)	4 (8%)	5 (10%)
Mineralization	4 (8%)	6 (12%)	7 (14%)
Necrosis	1 (2%)		
Interstitial cell, hyperplasia	3 (6%)	2 (4%)	4 (8%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Myelofibrosis	1 (2%)		
Necrosis	1 (2%)		
Lymph node	(2)	(4)	
Angiectasis	1 (50%)		
Congestion		1 (25%)	
Lymph node, mandibular	(50)	(50)	(50)
Hyperplasia		1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)
Amyloid deposition		1 (2%)	
Atrophy	2 (4%)		1 (2%)
Congestion		1 (2%)	
Ectasia	1 (2%)	2 (4%)	1 (2%)
Necrosis			1 (2%)
Spleen	(50)	(50)	(50)
Congestion	8 (16%)	5 (10%)	5 (10%)
Fibrosis	3 (6%)	3 (6%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)
Hemorrhage			1 (2%)
Pigmentation, hemosiderin	1 (2%)		
Lymphoid follicle, depletion cellular	1 (2%)		
Red pulp, hyperplasia	1 (2%)		
Thymus	(44)	(50)	(47)
Atrophy	7 (16%)		
Integumentary System			
Mammary gland	(50)	(50)	(49)
Dilatation	28 (56%)	34 (68%)	31 (63%)
Galactocele	6 (12%)	7 (14%)	9 (18%)
Hyperplasia	8 (16%)	9 (18%)	5 (10%)
Hyperplasia, cystic, focal			1 (2%)
Hyperplasia, focal	5 (10%)	8 (16%)	5 (10%)
Pigmentation, hemosiderin		1 (2%)	
Skin	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Hyperkeratosis	1 (2%)		
Parakeratosis	1 (2%)		
Epidermis, pinna, hyperplasia			1 (2%)
Epidermis, skin, site of application, hyperplasia		29 (58%)	44 (88%)
Pinna, parakeratosis			1 (2%)
Sebaceous gland, site of application, hyperplasia		27 (54%)	44 (88%)
Skin, site of application, edema			1 (2%)
Skin, site of application, hyperkeratosis		23 (46%)	25 (50%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System (continued)			
Skin (continued)	(50)	(50)	(50)
Skin, site of application, inflammation, chronic active		10 (20%)	28 (56%)
Skin, site of application, parakeratosis		21 (42%)	33 (66%)
Skin, site of application, ulcer		4 (8%)	25 (50%)
Subcutaneous tissue, fibrosis	1 (2%)		
Musculoskeletal System			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		1 (2%)
Osteosclerosis	1 (2%)		
Skeletal muscle			(1)
Hemorrhage			1 (100%)
Nervous System			
Brain	(50)	(50)	(50)
Hydrocephalus	1 (2%)		1 (2%)
Mineralization			1 (2%)
Vacuolization cytoplasmic		1 (2%)	1 (2%)
Respiratory System			
Lung	(50)	(50)	(50)
Cyst		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, chronic active	1 (2%)	3 (6%)	4 (8%)
Mineralization	21 (42%)	22 (44%)	34 (68%)
Alveolar epithelium, hyperplasia	1 (2%)		1 (2%)
Interstitium, fibrosis		2 (4%)	
Nose	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)
Inflammation, suppurative	11 (22%)	5 (10%)	3 (6%)
Special Senses System			
Eye		(1)	(2)
Mineralization			1 (50%)
Lens, mineralization		1 (100%)	1 (50%)
Urinary System			
Kidney	(50)	(50)	(50)
Cyst	7 (14%)	4 (8%)	6 (12%)
Fibrosis		1 (2%)	
Inflammation, chronic active	1 (2%)		
Mineralization	1 (2%)	1 (2%)	3 (6%)
Nephropathy	42 (84%)	40 (80%)	40 (80%)
Pigmentation, hemosiderin	2 (4%)	2 (4%)	
Renal tubule, regeneration	2 (4%)	1 (2%)	1 (2%)
Urinary bladder	(50)	(50)	(50)
Hemorrhage			1 (2%)
Necrosis			1 (2%)

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental deaths	1		1
Moribund	10	12	5
Natural deaths	11	12	22
Survivors			
Terminal sacrifice	28	26	22
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(45)	(46)	(43)
Intestine small, duodenum	(49)	(49)	(49)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Intestine small, jejunum	(42)	(43)	(38)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Liver	(50)	(50)	(50)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Mesentery	(5)	(2)	(4)
Carcinoma, metastatic, urinary bladder	1 (20%)		
Oral mucosa	(1)	(1)	
Squamous cell papilloma		1 (100%)	
Pancreas	(50)	(50)	(49)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Salivary glands	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(49)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Tongue		(1)	
Squamous cell papilloma		1 (100%)	
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Heart	(50)	(50)	(49)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma	1 (2%)		
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(50)	(50)	(49)
Adenoma		2 (4%)	
Carcinoma			1 (2%)
Parathyroid gland	(47)	(40)	(45)
Pituitary gland	(50)	(50)	(49)
Pars distalis, adenoma	22 (44%)	30 (60%)	30 (61%)
Pars distalis, adenoma, multiple	1 (2%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System (continued)			
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	1 (2%)	4 (8%)	3 (6%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma	1 (2%)	2 (4%)	1 (2%)
Follicular cell, carcinoma		1 (2%)	
General Body System			
None			
Genital System			
Clitoral gland	(49)	(48)	(48)
Adenoma	7 (14%)	6 (13%)	6 (13%)
Carcinoma	3 (6%)	3 (6%)	
Bilateral, adenoma			1 (2%)
Ovary	(50)	(50)	(50)
Granulosa cell tumor benign		1 (2%)	
Uterus	(50)	(50)	(50)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Leiomyosarcoma			1 (2%)
Polyp stromal	2 (4%)	5 (10%)	5 (10%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(3)	(3)	(1)
Lymph node, mandibular	(49)	(50)	(49)
Lymph node, mesenteric	(50)	(50)	(50)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Spleen	(50)	(50)	(50)
Thymus	(44)	(49)	(48)
Integumentary System			
Mammary gland	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	2 (4%)
Carcinoma		2 (4%)	3 (6%)
Fibroadenoma	11 (22%)	11 (22%)	9 (18%)
Fibroadenoma, multiple		1 (2%)	
Skin	(50)	(50)	(50)
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)	
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, lipoma			1 (2%)
Musculoskeletal System			
Skeletal muscle	(2)		
Carcinoma, metastatic, urinary bladder	1 (50%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg
Nervous System			
Brain	(50)	(50)	(50)
Glioma malignant		1 (2%)	
Hemangioma		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Carcinoma, metastatic, urinary bladder	1 (2%)		
Squamous cell carcinoma	1 (2%)		
Special Senses System			
Zymbal's gland			(1)
Carcinoma			1 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Carcinoma, metastatic, urinary bladder	1 (2%)		
Squamous cell carcinoma, metastatic, lung	1 (2%)		
Renal tubule, adenoma	1 (2%)		
Urinary bladder	(49)	(49)	(47)
Transitional epithelium, carcinoma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia mononuclear	10 (20%)	6 (12%)	5 (10%)
Lymphoma malignant	1 (2%)	1 (2%)	
Mesothelioma malignant	1 (2%)		
Neoplasm Summary			
Total animals with primary neoplasms[c]	40	41	38
Total primary neoplasms	69	83	70
Total animals with benign neoplasms	33	39	37
Total benign neoplasms	51	69	58
Total animals with malignant neoplasms	18	13	12
Total malignant neoplasms	18	14	12
Total animals with metastatic neoplasms	2		
Total metastatic neoplasms	12		

[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 Lauric Acid Diethanolamine Condensate: Vehicle Control

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

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

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

Number of Days on Study	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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 8	1 5 9	1 6 0	1 6 5	1 6 6	1 7 2	1 7 5	1 8 0	1 8 3	1 8 4	1 8 7	1 8 8	1 9 2	1 9 7	1 5 5	1 6 4	1 6 7	1 7 0	1 7 1	1 7 3	1 7 7	1 7 8	1 8 6	1 9 6	1 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, urinary bladder																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Carcinoma, metastatic, urinary bladder																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																										1
Mesentery																										5
Carcinoma, metastatic, urinary bladder																										1
Oral mucosa							+																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X				X	X					X					X	X	X	X	X	X	22
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma															X											1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X							X					X	X				X					X		7
Carcinoma	X																				X					3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																										1
Polyp stromal			X																					X		2

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

Number of Days on Study	2 1 9	3 2 2	3 7 4	4 1 6	4 7 1	4 7 5	4 7 9	4 9 9	5 2 1	5 2 7	5 6 4	6 1 7	6 4 0	6 5 4	6 6 2	6 6 7	6 6 9	6 8 2	6 8 8	6 9 1	6 9 4	7 0 7	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 6 1	1 6 3	2 0 0	1 5 2	1 9 9	1 5 1	1 6 8	1 9 3	1 7 4	1 6 9	1 8 9	1 8 2	1 5 7	1 9 0	1 7 9	1 6 2	1 9 5	1 8 1	1 8 5	1 9 4	1 7 6	1 9 1	1 5 3	1 5 4	1 5 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																+	+		+						
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma								X				X			X									X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma							X										X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+															+								
Carcinoma, metastatic, urinary bladder		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																					
Carcinoma, metastatic, urinary bladder		X																							
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder		X																							
Squamous cell carcinoma, metastatic, lung																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X							X		X	X					X		X	X			X			
Lymphoma malignant																									
Mesothelioma malignant																	X								

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

Number of Days on Study	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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 8	1 5 9	1 6 0	1 6 5	1 6 6	1 7 2	1 7 5	1 8 0	1 8 3	1 8 4	1 8 7	1 8 8	1 9 2	1 9 7	1 5 5	1 6 4	1 6 7	1 7 0	1 7 1	1 7 3	1 7 7	1 7 8	1 8 6	1 9 6	1 9 8	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	44
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X							1
Fibroadenoma										X		X	X					X		X	X		X				11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																											2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											2
Carcinoma, metastatic, urinary bladder																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											1
Carcinoma, metastatic, urinary bladder																											1
Squamous cell carcinoma		X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, urinary bladder																											1
Squamous cell carcinoma, metastatic, lung		X																									1
Renal tubule, adenoma		X																									1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X						X				10
Lymphoma malignant												X															1
Mesothelioma malignant																											1

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

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

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	208	213	223	225	226	231	235	237	239	243	244	245	248	249	211	215	218	219	227	229	230	234	236	240	246	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+		+																					2
Oral mucosa							+																			1
Squamous cell papilloma							X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X													X												2
Parathyroid gland	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X				X	X	X	X	X	X	X			X	X		X	X		X	X	X	30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X											X								4
Follicular cell, adenoma										X												X				2
Follicular cell, carcinoma													X													1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Adenoma					X			X	X				X													6
Carcinoma																	X									3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X		X																				5

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

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

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	208	213	223	225	226	231	235	237	239	243	244	245	248	249	211	215	218	219	227	229	230	234	236	240	246	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma								X		X																2
Fibroadenoma	X								X														X	X		11
Fibroadenoma, multiple																									X	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Hemangioma																										1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																										1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									6
Lymphoma malignant																										1

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

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

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

Number of Days on Study	7 2 2	7 2 4	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 9	2 7 1	2 9 9	2 5 4	2 5 5	2 5 7	2 6 2	2 6 4	2 6 5	2 6 9	2 7 5	2 7 6	2 7 9	2 9 0	2 9 3	2 9 4	2 6 1	2 6 3	2 6 7	2 7 2	2 7 7	2 8 4	2 8 6	2 8 7	3 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	A	A	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	A	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+									+														4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X	X	X	X	X	X	X	X		X		X	X	X		X	X		X	X		30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X							X															3
Follicular cell, adenoma																									X	1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X													X						X	X		X	6
Bilateral, adenoma																		X								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma		X																								1
Polyp stromal			X			X												X					X			5
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

Number of Days on Study	0 3 6	3 2 3	3 4 7	3 6 1	3 6 3	3 6 4	3 9 8	4 2 7	4 6 5	5 0 7	5 2 5	5 3 5	5 8 8	5 9 4	5 9 5	6 0 2	6 3 4	6 3 9	6 4 6	6 5 5	6 8 0	6 8 4	6 9 3	7 0 1	7 0 3
Carcass ID Number	2 9 6	2 9 7	2 7 0	2 5 8	2 8 0	2 6 6	2 5 2	2 7 4	2 6 0	2 8 3	2 6 8	2 9 2	2 8 8	2 8 1	2 9 5	2 8 9	2 5 1	2 7 8	2 8 5	2 7 3	2 5 3	2 9 8	2 8 2	2 9 1	2 5 6
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																	X				X				
Fibroadenoma												X		X	X						X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																				+					
Spinal cord																				+					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																	+	+
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											X

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

Number of Days on Study	7 2 2	7 2 4	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 9	2 7 1	2 9 9	2 5 4	2 5 5	2 5 7	2 6 2	2 6 4	2 6 5	2 6 9	2 7 5	2 7 6	2 7 9	2 9 0	2 9 3	2 9 4	2 6 1	2 6 3	2 6 7	2 7 2	2 7 7	2 8 4	2 8 6	2 8 7	3 0 0	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X								X					2
Carcinoma																								X		3
Fibroadenoma						X	X		X			X													X	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																	+	+					6
Zymbal's gland				+																						1
Carcinoma				X																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X	X											X			5

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

	Vehicle Control	50 mg/kg	100 mg/kg
Clitoral Gland: Adenoma			
Overall rate[a]	7/49 (14%)	6/48 (13%)	7/48 (15%)
Adjusted rate[b]	18.1%	15.7%	20.1%
Terminal rate[c]	6/27 (22%)	4/25 (16%)	5/21 (24%)
First incidence (days)	617	627	701
Poly-3 test[d]	P=0.483	P=0.512N	P=0.530
Clitoral Gland: Carcinoma			
Overall rate	3/49 (6%)	3/48 (6%)	0/48 (0%)
Adjusted rate	7.8%	7.9%	0.0%
Terminal rate	3/27 (11%)	2/25 (8%)	0/21 (0%)
First incidence (days)	729 (T)	696	—[e]
Poly-3 test	P=0.125N	P=0.658	P=0.136N
Clitoral Gland: Adenoma or Carcinoma			
Overall rate	10/49 (20%)	9/48 (19%)	7/48 (15%)
Adjusted rate	25.8%	23.5%	20.1%
Terminal rate	9/27 (33%)	6/25 (24%)	5/21 (24%)
First incidence (days)	617	627	701
Poly-3 test	P=0.334N	P=0.512N	P=0.381N
Mammary Gland: Fibroadenoma			
Overall rate	11/50 (22%)	12/50 (24%)	9/50 (18%)
Adjusted rate	27.0%	28.9%	23.6%
Terminal rate	8/28 (29%)	6/26 (23%)	5/22 (23%)
First incidence (days)	499	458	535
Poly-3 test	P=0.422N	P=0.525	P=0.464N
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	11/50 (22%)	14/50 (28%)	11/50 (22%)
Adjusted rate	27.0%	32.9%	28.8%
Terminal rate	8/28 (29%)	6/26 (23%)	7/22 (32%)
First incidence (days)	499	458	535
Poly-3 test	P=0.472	P=0.365	P=0.529
Mammary Gland: Carcinoma			
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	5.1%	8.1%
Terminal rate	0/28 (0%)	2/26 (8%)	1/22 (5%)
First incidence (days)	—	729 (T)	634
Poly-3 test	P=0.072	P=0.235	P=0.107
Mammary Gland: Adenoma or Carcinoma			
Overall rate	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	2.5%	10.0%	13.5%
Terminal rate	1/28 (4%)	2/26 (8%)	3/22 (14%)
First incidence (days)	729 (T)	534	634
Poly-3 test	P=0.066	P=0.183	P=0.085

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

	Vehicle Control	50 mg/kg	100 mg/kg
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	11/50 (22%)	16/50 (32%)	13/50 (26%)
Adjusted rate	27.0%	37.6%	33.8%
Terminal rate	8/28 (29%)	8/26 (31%)	8/22 (36%)
First incidence (days)	499	458	535
Poly-3 test	P=0.293	P=0.211	P=0.340
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	23/50 (46%)	30/50 (60%)	30/49 (61%)
Adjusted rate	55.8%	69.8%	73.2%
Terminal rate	16/28 (57%)	19/26 (73%)	17/22 (77%)
First incidence (days)	564	489	398
Poly-3 test	P=0.050	P=0.122	P=0.066
Thyroid Gland (C-cell): Adenoma			
Overall rate	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate	2.5%	10.0%	8.2%
Terminal rate	0/28 (0%)	2/26 (8%)	2/22 (9%)
First incidence (days)	707	534	655
Poly-3 test	P=0.220	P=0.180	P=0.279
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	5.1%	10.0%	8.2%
Terminal rate	1/28 (4%)	2/26 (8%)	2/22 (9%)
First incidence (days)	707	534	655
Poly-3 test	P=0.379	P=0.340	P=0.467
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.5%	7.7%	2.7%
Terminal rate	1/28 (4%)	3/26 (12%)	1/22 (5%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.575	P=0.302	P=0.744
Uterus: Stromal Polyp			
Overall rate	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate	5.1%	12.4%	13.6%
Terminal rate	2/28 (7%)	2/26 (8%)	3/22 (14%)
First incidence (days)	729 (T)	582	634
Poly-3 test	P=0.150	P=0.224	P=0.187
All Organs: Mononuclear Cell Leukemia			
Overall rate	10/50 (20%)	6/50 (12%)	5/50 (10%)
Adjusted rate	23.3%	14.8%	13.5%
Terminal rate	2/28 (7%)	2/26 (8%)	3/22 (14%)
First incidence (days)	219	582	594
Poly-3 test	P=0.150N	P=0.237N	P=0.202N

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

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Benign Neoplasms			
Overall rate	33/50 (66%)	39/50 (78%)	37/50 (74%)
Adjusted rate	75.5%	86.5%	87.9%
Terminal rate	22/28 (79%)	23/26 (89%)	20/22 (91%)
First incidence (days)	416	458	398
Poly-3 test	P=0.062	P=0.125	P=0.094
All Organs: Malignant Neoplasms			
Overall rate	18/50 (36%)	13/50 (26%)	12/50 (24%)
Adjusted rate	40.9%	31.2%	31.3%
Terminal rate	8/28 (29%)	6/26 (23%)	5/22 (23%)
First incidence (days)	219	575	465
Poly-3 test	P=0.198N	P=0.235N	P=0.246N
All Organs: Benign or Malignant Neoplasms			
Overall rate	40/50 (80%)	41/50 (82%)	38/50 (76%)
Adjusted rate	85.5%	89.1%	88.7%
Terminal rate	23/28 (82%)	23/26 (89%)	20/22 (91%)
First incidence (days)	219	458	398
Poly-3 test	P=0.368	P=0.411	P=0.441

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental deaths	1		1
Moribund	10	12	5
Natural deaths	11	12	22
Survivors			
Terminal sacrifice	28	26	22
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(45)	(46)	(43)
Parasite metazoan	2 (4%)	4 (9%)	3 (7%)
Intestine large, rectum	(42)	(45)	(43)
Inflammation, chronic active			1 (2%)
Parasite metazoan	2 (5%)	2 (4%)	1 (2%)
Intestine large, cecum	(40)	(40)	(31)
Inflammation, chronic active		1 (3%)	
Intestine small, duodenum	(49)	(49)	(49)
Inflammation, chronic active		1 (2%)	
Ulcer			1 (2%)
Intestine small, jejunum	(42)	(43)	(38)
Mineralization		1 (2%)	
Intestine small, ileum	(48)	(42)	(37)
Parasite metazoan			1 (3%)
Liver	(50)	(50)	(50)
Basophilic focus	1 (2%)		1 (2%)
Clear cell focus	1 (2%)	3 (6%)	2 (4%)
Eosinophilic focus		3 (6%)	2 (4%)
Hepatodiaphragmatic nodule	12 (24%)	17 (34%)	12 (24%)
Inflammation, chronic active	13 (26%)	15 (30%)	4 (8%)
Mixed cell focus		1 (2%)	
Necrosis		4 (8%)	
Vacuolization cytoplasmic	3 (6%)	6 (12%)	2 (4%)
Bile duct, hyperplasia		1 (2%)	
Central vein, dilatation		1 (2%)	
Hepatocyte, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Mesentery	(5)	(2)	(4)
Necrosis		1 (50%)	
Fat, inflammation, chronic active	4 (80%)	1 (50%)	3 (75%)
Fat, mineralization			2 (50%)
Oral mucosa	(1)	(1)	
Hyperplasia	1 (100%)		
Pancreas	(50)	(50)	(49)
Inflammation, chronic active			1 (2%)
Necrosis		1 (2%)	
Acinus, atrophy	3 (6%)	5 (10%)	1 (2%)
Arteriole, thrombosis			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 Lauric Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Stomach, forestomach	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic active		2 (4%)	2 (4%)
Ulcer	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(49)
Erosion	3 (6%)		
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)
Heart	(50)	(50)	(49)
Hemorrhage			1 (2%)
Mineralization		1 (2%)	
Myocardium, inflammation, chronic active	27 (54%)	31 (62%)	35 (71%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	2 (4%)	2 (4%)	3 (6%)
Angiectasis	2 (4%)		
Degeneration	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)
Hypertrophy		1 (2%)	
Mineralization		1 (2%)	
Necrosis	1 (2%)		1 (2%)
Vacuolization cytoplasmic	5 (10%)	4 (8%)	7 (14%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia			1 (2%)
Parathyroid gland	(47)	(40)	(45)
Hyperplasia	1 (2%)		2 (4%)
Pituitary gland	(50)	(50)	(49)
Cyst	8 (16%)	5 (10%)	3 (6%)
Hemorrhage			1 (2%)
Hyperplasia	4 (8%)		2 (4%)
Thrombosis	1 (2%)		
Pars distalis, angiectasis	1 (2%)	2 (4%)	
Pars distalis, hyperplasia	1 (2%)	2 (4%)	
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia	2 (4%)	5 (10%)	3 (6%)
Follicle, cyst		1 (2%)	
General Body System			
None			

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

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System			
Clitoral gland	(49)	(48)	(48)
Cyst	4 (8%)		1 (2%)
Inflammation, chronic active	30 (61%)	34 (71%)	36 (75%)
Mineralization		1 (2%)	
Necrosis			1 (2%)
Ovary	(50)	(50)	(50)
Follicle, cyst	3 (6%)	1 (2%)	1 (2%)
Periovarian tissue, cyst	5 (10%)	8 (16%)	5 (10%)
Uterus	(50)	(50)	(50)
Congestion			1 (2%)
Cyst			1 (2%)
Hemorrhage	1 (2%)		
Hydrometra	4 (8%)	4 (8%)	8 (16%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Inflammation, chronic active		2 (4%)	
Myelofibrosis		1 (2%)	
Lymph node	(3)	(3)	(1)
Hemorrhage		1 (33%)	
Pigmentation, hemosiderin	1 (33%)		
Lymph node, mandibular	(49)	(50)	(49)
Atrophy	1 (2%)		
Hemorrhage		1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)
Ectasia		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Pigmentation, lipofuscin		2 (4%)	4 (8%)
Arteriole, inflammation, chronic active			1 (2%)
Spleen	(50)	(50)	(50)
Angiectasis			1 (2%)
Congestion	1 (2%)	1 (2%)	1 (2%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation		1 (2%)	
Necrosis	1 (2%)	1 (2%)	
Pigmentation, hemosiderin	1 (2%)		
Thrombosis	3 (6%)		
Thymus	(44)	(49)	(48)
Atrophy	2 (5%)	1 (2%)	
Hemorrhage			1 (2%)
Integumentary System			
Mammary gland	(50)	(50)	(50)
Dilatation	35 (70%)	40 (80%)	32 (64%)
Fibrosis	1 (2%)		
Galactocele	1 (2%)		
Hyperplasia, cystic, focal	1 (2%)		
Hyperplasia, focal	2 (4%)	3 (6%)	2 (4%)
Skin	(50)	(50)	(50)
Parakeratosis		1 (2%)	1 (2%)
Epidermis, skin, site of application, hyperplasia	5 (10%)	33 (66%)	44 (88%)
Sebaceous gland, skin, site of application, hyperplasia	3 (6%)	41 (82%)	45 (90%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System (continued)			
Skin (continued)	(50)	(50)	(50)
Skin, site of application, hyperkeratosis		20 (40%)	29 (58%)
Skin, site of application, inflammation, chronic active	3 (6%)	35 (70%)	34 (68%)
Skin, site of application, parakeratosis	2 (4%)	12 (24%)	25 (50%)
Skin, site of application, ulcer	3 (6%)	2 (4%)	10 (20%)
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Hemorrhage		2 (4%)	
Inflammation, chronic active		1 (2%)	
Spinal cord	(1)		(1)
Hemorrhage	1 (100%)		
Respiratory System			
Lung	(50)	(50)	(50)
Congestion		1 (2%)	3 (6%)
Hemorrhage			2 (4%)
Inflammation, chronic active	2 (4%)	2 (4%)	8 (16%)
Mineralization	23 (46%)	18 (36%)	19 (38%)
Interstitium, fibrosis	2 (4%)	2 (4%)	
Nose	(50)	(50)	(50)
Inflammation, suppurative	4 (8%)	1 (2%)	2 (4%)
Special Senses System			
Eye	(1)	(1)	(6)
Cataract			1 (17%)
Synechia		1 (100%)	
Lens, mineralization	1 (100%)		3 (50%)
Posterior chamber, hemorrhage			1 (17%)
Retina, degeneration	1 (100%)		1 (17%)
Urinary System			
Kidney	(50)	(50)	(50)
Cyst	2 (4%)		2 (4%)
Inflammation, chronic active			2 (4%)
Mineralization	24 (48%)	23 (46%)	27 (54%)
Necrosis			1 (2%)
Nephropathy	40 (80%)	41 (82%)	40 (80%)
Pigmentation, hemosiderin	2 (4%)	2 (4%)	2 (4%)
Renal tubule, regeneration	2 (4%)	4 (8%)	2 (4%)
Urinary bladder	(49)	(49)	(47)
Inflammation, chronic active		3 (6%)	
Mineralization		1 (2%)	
Pigmentation, hemosiderin			1 (2%)

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	7	6	7
Natural deaths	3	7	2
Survivors			
Terminal sacrifice	40	37	41
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(47)	(49)	(49)
Intestine small, duodenum	(50)	(50)	(49)
Polyp adenomatous	1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)
Epithelium, carcinoma		1 (2%)	
Liver	(50)	(50)	(50)
Carcinoid tumor malignant, metastatic, stomach, forestomach			1 (2%)
Carcinoid tumor malignant, metastatic, stomach, glandular		1 (2%)	
Carcinoma, metastatic, islets, pancreatic	1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)
Hemangiosarcoma	7 (14%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	8 (16%)	8 (16%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)		1 (2%)
Hepatocellular adenoma	13 (26%)	22 (44%)	15 (30%)
Hepatocellular adenoma, multiple	6 (12%)	4 (8%)	10 (20%)
Hepatocholangiocarcinoma		1 (2%)	
Pancreas	(50)	(50)	(50)
Acinus, hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)
Carcinoid tumor malignant		1 (2%)	
Serosa, carcinoid tumor malignant, metastatic, stomach, glandular			1 (2%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		

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

	Vehicle Control	100 mg/kg	200 mg/kg
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma	1 (2%)	4 (8%)	
Capsule, adenoma	1 (2%)	3 (6%)	1 (2%)
Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)
Adenoma		2 (4%)	1 (2%)
Carcinoma	1 (2%)		
Pituitary gland	(48)	(49)	(50)
Pars distalis, adenoma		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)	4 (8%)	2 (4%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Prostate	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland			1 (2%)
Seminal vesicle	(50)	(50)	(50)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)	
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Lymph node	(3)	(2)	(1)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (33%)		
Mediastinal, carcinoma, metastatic, mammary gland			1 (100%)
Lymph node, mandibular	(46)	(45)	(46)
Lymph node, mesenteric	(49)	(49)	(50)
Carcinoma, metastatic, mammary gland			1 (2%)
Hemangiosarcoma	1 (2%)		
Spleen	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		2 (4%)
Thymus	(45)	(45)	(49)
Hemangioma	1 (2%)		
Integumentary System			
Mammary gland	(5)		(1)
Carcinoma			1 (100%)
Musculoskeletal System			
None			

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

	Vehicle Control	100 mg/kg	200 mg/kg
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	5 (10%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	6 (12%)	8 (16%)	6 (12%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)		
Carcinoma, metastatic, islets, pancreatic	1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)
Hemangiosarcoma, metastatic, liver	1 (2%)	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Bronchiole, adenoma	1 (2%)		
Nose	(50)	(50)	(50)
Special Senses System			
Harderian gland	(1)	(2)	(3)
Adenoma	1 (100%)	2 (100%)	3 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland			1 (2%)
Renal tubule, adenoma		1 (2%)	1 (2%)
Ureter	(1)		
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Lymphoma malignant	4 (8%)	3 (6%)	2 (4%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	45	44	42
Total primary neoplasms	67	76	69
Total animals with benign neoplasms	27	36	35
Total benign neoplasms	32	51	43
Total animals with malignant neoplasms	29	23	22
Total malignant neoplasms	35	25	26
Total animals with metastatic neoplasms	5	5	6
Total metastatic neoplasms	8	6	13

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

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

Number of Days on Study	3 4 4	3 5 3	5 4 1	5 6 2	5 8 4	6 1 6	6 2 2	6 3 6	6 4 6	6 7 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 5 0	0 0 7	0 2 8	0 3 2	0 1 5	0 4 5	0 1 8	0 3 7	0 4 4	0 1 1	0 0 2	0 0 4	0 0 6	0 1 3	0 1 7	0 1 9	0 2 2	0 2 9	0 3 1	0 3 3	0 3 4	0 3 6	0 3 8	0 4 2	0 4 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreatic islets					X																				
Hemangiosarcoma				X				X		X	X					X									
Hepatocellular carcinoma		X				X	X								X								X		
Hepatocellular carcinoma, multiple			X														X								
Hepatocellular adenoma										X		X								X	X		X		X
Hepatocellular adenoma, multiple																						X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Parathyroid gland	+	+	M	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS													+												
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Lauric Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 4 7	0 4 8	0 4 9	0 0 1	0 0 3	0 0 5	0 0 8	0 0 9	0 1 0	0 1 2	0 1 4	0 1 6	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 3 0	0 3 5	0 3 9	0 4 0	0 4 1	0 4 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous										X																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreatic islets																										1
Hemangiosarcoma						X																X				7
Hepatocellular carcinoma			X												X			X								8
Hepatocellular carcinoma, multiple												X														3
Hepatocellular adenoma	X		X					X	X		X			X										X		13
Hepatocellular adenoma, multiple		X		X		X											X		X							6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Capsule, adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma								X																		1
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	3 4 4	3 5 3	5 4 1	5 6 2	5 8 4	6 1 6	6 2 2	6 3 6	6 4 6	6 7 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 5 0	0 0 7	0 2 8	0 3 2	0 1 5	0 4 5	0 1 8	0 3 7	0 4 4	0 1 1	0 0 2	0 0 4	0 0 6	0 1 3	0 1 7	0 1 9	0 2 2	0 2 9	0 3 1	0 3 3	0 3 4	0 3 6	0 3 8	0 4 2	0 4 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Lymph node	+					+																			
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+
Hemangioma																									
Integumentary System																									
Mammary gland	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X											X	
Alveolar/bronchiolar adenoma, multiple									X																
Alveolar/bronchiolar carcinoma														X				X			X				
Alveolar/bronchiolar carcinoma, multiple						X											X								
Carcinoma, metastatic, pancreatic islets					X																				
Hemangiosarcoma, metastatic, liver								X																	
Hepatocellular carcinoma, metastatic, liver						X											X								
Bronchiole, adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter									+																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X								X																

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 4 7	0 4 8	0 4 9	0 0 1	0 0 3	0 0 5	0 0 8	0 0 9	0 1 0	0 1 2	0 1 4	0 1 6	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 3 0	0 3 5	0 3 9	0 4 0	0 4 1	0 4 3	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																												1
Lymph node																									+			3
Mediastinal alveolar/bronchiolar carcinoma, metastatic, lung																												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																								2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Hemangioma									X																			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			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Alveolar/bronchiolar adenoma							X														X							5
Alveolar/bronchiolar adenoma, multiple																												1
Alveolar/bronchiolar carcinoma				X						X									X									6
Alveolar/bronchiolar carcinoma, multiple																												2
Carcinoma, metastatic, pancreatic islets																												1
Hemangiosarcoma, metastatic, liver																												1
Hepatocellular carcinoma, metastatic, liver												X																3
Bronchiole, adenoma							X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Special Senses System																												
Harderian gland							+																					1
Adenoma							X																					1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Ureter																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Lymphoma malignant														X										X				4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	1 6 4	4 1 5	4 6 2	5 2 8	5 9 5	6 2 6	6 3 7	6 3 8	6 6 8	7 0 6	7 0 6	7 1 7	7 1 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 6 0	0 7 1	0 8 7	0 9 5	0 6 3	0 8 4	0 9 7	0 7 6	0 6 2	0 6 5	0 7 2	0 5 2	0 9 4	0 5 6	0 5 9	0 6 1	0 6 7	0 6 8	0 6 9	0 7 4	0 7 5	0 7 8	0 7 9	0 8 3	0 8 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epithelium, carcinoma																X									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant, metastatic, stomach, glandular								X																	
Hemangiosarcoma										X															
Hepatocellular carcinoma						X					X														
Hepatocellular adenoma				X	X	X	X					X	X								X	X	X		
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma				X																					
Mesentery		+																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, hepatocholangiocarcinoma, metastatic, liver				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant								X																	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Capsule, adenoma																							X		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																				X					
Pheochromocytoma benign			X																						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	+	+	+	M	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 8 8	0 8 9	0 9 0	0 9 1	0 9 8	0 9 9	0 5 1	0 5 3	0 5 4	0 5 5	0 5 7	0 5 8	0 6 4	0 6 6	0 7 0	0 7 3	0 7 7	0 8 0	0 8 1	0 8 2	0 8 5	0 9 2	0 9 3	0 9 6	1 0 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
Epithelium, carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant, metastatic, stomach, glandular																										1
Hemangiosarcoma	X																									2
Hepatocellular carcinoma		X	X		X							X				X			X							8
Hepatocellular adenoma		X			X	X	X				X	X	X		X		X			X	X	X		X		22
Hepatocellular adenoma, multiple	X							X											X				X			4
Hepatocholangiocarcinoma																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X												X							X			4
Capsule, adenoma										X														X		3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				2
Parathyroid gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X					X									X										X	4
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	1 6 4	4 1 5	4 6 2	5 2 8	5 9 5	6 2 6	6 3 7	6 3 8	6 6 8	7 0 6	7 0 6	7 1 7	7 1 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 6 0	0 7 1	0 8 7	0 9 5	0 6 3	0 8 4	0 9 7	0 7 6	0 6 2	0 6 5	0 7 2	0 5 2	0 9 4	0 5 6	0 5 9	0 6 1	0 6 7	0 6 8	0 6 9	0 7 4	0 7 5	0 7 8	0 7 9	0 8 3	0 8 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+										+						
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma									X				X			X					X				
Hemangiosarcoma, metastatic, liver										X															
Hepatocellular carcinoma, metastatic, liver											X														
Hepatocholangiocarcinoma, metastatic, liver				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland								+																	
Adenoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X								X										X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID number	0 8 8	0 8 9	0 9 0	0 9 1	0 9 8	0 9 9	0 5 1	0 5 3	0 5 4	0 5 5	0 5 7	0 5 8	0 6 4	0 6 6	0 7 0	0 7 3	0 7 7	0 8 0	0 8 1	0 8 2	0 8 5	0 9 2	0 9 3	0 9 6	1 0 0	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X											X									X	X				5
Alveolar/bronchiolar adenoma, multiple		X																								1
Alveolar/bronchiolar carcinoma										X					X			X					X			8
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver			X																							2
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																						+				2
Adenoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	14 40	14 44	14 45	14 46	14 48	14 49	15 00	10 01	10 09	11 12	11 15	11 18	12 22	12 24	12 29	13 00	13 32	13 33	13 36	13 37	13 39	14 41	14 42	14 43	14 47	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant, metastatic, stomach, forestomach					X																					1
Carcinoma, metastatic, mammary gland																										1
Hemangiosarcoma																			X							3
Hepatocellular carcinoma										X		X		X											X	11
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X		X			X	X					X								X	X	X		X	15
Hepatocellular adenoma, multiple						X				X	X			X		X			X							10
Mesentery		+														+										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, carcinoid tumor malignant					X																					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																					X					2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	4 4 4	4 9 2	5 1 9	5 5 4	5 6 0	5 7 3	6 1 1	6 4 3	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 1 7	1 1 9	1 3 4	1 1 0	1 2 1	1 2 6	1 1 4	1 2 8	1 2 3	1 0 2	1 0 3	1 0 4	1 0 5	1 0 6	1 0 7	1 0 8	1 1 1	1 1 3	1 1 6	1 2 0	1 2 5	1 2 7	1 3 1	1 3 5	1 3 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+																			
Mediastinal, carcinoma, metastatic, mammary gland						X																			
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X							X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Carcinoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve									+																
Spinal cord									+																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X		X	X																
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma										X					X										
Carcinoma, metastatic, mammary gland						X																			
Hepatocellular carcinoma, metastatic, liver	X	X					X																	X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Harderian gland																							+		
Adenoma																							X		
Lacrimal gland							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland						X																			
Renal tubule, adenoma																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 Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 4 0	1 4 4	1 4 5	1 4 6	1 4 8	1 4 9	1 5 0	1 0 1	1 0 9	1 1 2	1 1 5	1 1 8	1 2 2	1 2 4	1 2 9	1 3 0	1 3 2	1 3 3	1 3 6	1 3 7	1 3 9	1 4 1	1 4 2	1 4 3	1 4 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Mediastinal, carcinoma, metastatic, mammary gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X							X							X			X			X		X		9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma					X		X	X																	X	6
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver																										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+		+						3
Harderian gland																		+		+						3
Adenoma																		X		X						3
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Renal tubule, adenoma																										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 Lauric Acid Diethanolamine Condensate

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Cortex: Adenoma			
Overall rate[a]	2/50 (4%)	7/50 (14%)	1/50 (2%)
Adjusted rate[b]	4.5%	15.7%	2.2%
Terminal rate[c]	2/40 (5%)	7/37 (19%)	1/41 (2%)
First incidence (days)	735 (T)	735 (T)	735 (T)
Poly-3 test[d]	P=0.409N	P=0.077	P=0.495N
Harderian Gland: Adenoma			
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.2%	4.4%	6.6%
Terminal rate	1/40 (3%)	1/37 (3%)	3/41 (7%)
First incidence (days)	735 (T)	638	735 (T)
Poly-3 test	P=0.227	P=0.501	P=0.310
Liver: Hemangiosarcoma			
Overall rate	7/50 (14%)	2/50 (4%)	3/50 (6%)
Adjusted rate	15.2%	4.5%	6.4%
Terminal rate	4/40 (10%)	1/37 (3%)	1/41 (2%)
First incidence (days)	562	706	519
Poly-3 test	P=0.094N	P=0.085N	P=0.152N
Liver: Hepatocellular Adenoma			
Overall rate	19/50 (38%)	26/50 (52%)	25/50 (50%)
Adjusted rate	42.1%	55.8%	54.3%
Terminal rate	18/40 (45%)	20/37 (54%)	24/41 (59%)
First incidence (days)	670	528	554
Poly-3 test	P=0.145	P=0.133	P=0.166
Liver: Hepatocellular Carcinoma			
Overall rate	11/50 (22%)	8/50 (16%)	12/50 (24%)
Adjusted rate	23.3%	17.7%	24.6%
Terminal rate	7/40 (18%)	6/37 (16%)	6/41 (15%)
First incidence (days)	353	626	444
Poly-3 test	P=0.484	P=0.342N	P=0.537
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	28/50 (56%)	29/50 (58%)	32/50 (64%)
Adjusted rate	59.1%	62.1%	65.6%
Terminal rate	23/40 (58%)	22/37 (60%)	26/41 (63%)
First incidence (days)	353	528	444
Poly-3 test	P=0.288	P=0.467	P=0.326
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	6/50 (12%)	6/50 (12%)	10/50 (20%)
Adjusted rate	13.3%	13.4%	21.6%
Terminal rate	5/40 (13%)	6/37 (16%)	7/41 (17%)
First incidence (days)	646	735 (T)	573
Poly-3 test	P=0.172	P=0.613	P=0.221

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	8/50 (16%)	8/50 (16%)	6/50 (12%)
Adjusted rate	17.7%	17.8%	13.2%
Terminal rate	7/40 (18%)	6/37 (16%)	6/41 (15%)
First incidence (days)	616	668	735 (T)
Poly-3 test	P=0.332N	P=0.603	P=0.383N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	14/50 (28%)	14/50 (28%)	16/50 (32%)
Adjusted rate	30.7%	31.1%	34.5%
Terminal rate	12/40 (30%)	12/37 (32%)	13/41 (32%)
First incidence (days)	616	668	573
Poly-3 test	P=0.389	P=0.573	P=0.433
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.2%	9.0%	4.3%
Terminal rate	1/40 (3%)	4/37 (11%)	1/41 (2%)
First incidence (days)	735 (T)	735 (T)	519
Poly-3 test	P=0.424	P=0.177	P=0.510
All Organs: Hemangiosarcoma			
Overall rate	8/50 (16%)	2/50 (4%)	5/50 (10%)
Adjusted rate	17.4%	4.5%	10.7%
Terminal rate	5/40 (13%)	1/37 (3%)	3/41 (7%)
First incidence (days)	562	706	519
Poly-3 test	P=0.195N	P=0.049N	P=0.266N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	9/50 (18%)	2/50 (4%)	5/50 (10%)
Adjusted rate	19.6%	4.5%	10.7%
Terminal rate	6/40 (15%)	1/37 (3%)	3/41 (7%)
First incidence (days)	562	706	519
Poly-3 test	P=0.121N	P=0.028N	P=0.184N
All Organs: Malignant Lymphoma			
Overall rate	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	8.7%	6.5%	4.4%
Terminal rate	2/40 (5%)	1/37 (3%)	2/41 (5%)
First incidence (days)	344	164	735 (T)
Poly-3 test	P=0.271N	P=0.502N	P=0.343N
All Organs: Benign Neoplasms			
Overall rate	27/50 (54%)	36/50 (72%)	35/50 (70%)
Adjusted rate	59.5%	75.4%	73.6%
Terminal rate	25/40 (63%)	28/37 (76%)	30/41 (73%)
First incidence (days)	646	462	519
Poly-3 test	P=0.085	P=0.071	P=0.103

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

	Vehicle Control	100 mg/kg	200 mg/kg
All Organs: Malignant Neoplasms			
Overall rate	29/50 (58%)	23/50 (46%)	22/50 (44%)
Adjusted rate	58.0%	48.4%	44.0%
Terminal rate	19/40 (48%)	15/37 (41%)	14/41 (34%)
First incidence (days)	344	164	444
Poly-3 test	P=0.095N	P=0.227N	P=0.115N
All Organs:: Benign or Malignant Neoplasms			
Overall rate	45/50 (90%)	44/50 (88%)	42/50 (84%)
Adjusted rate	90.0%	89.5%	84.0%
Terminal rate	35/40 (88%)	32/37 (87%)	33/41 (81%)
First incidence (days)	344	164	444
Poly-3 test	P=0.222N	P=0.596N	P=0.277N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, 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**.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	7	6	7
Natural deaths	3	7	2
Survivors			
Terminal sacrifice	40	37	41
Animals examined microscopically	50	50	50
Alimentary System			
Intestine small, jejunum	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid			1 (2%)
Liver	(50)	(50)	(50)
Basophilic focus	1 (2%)	2 (4%)	1 (2%)
Clear cell focus	14 (28%)	7 (14%)	6 (12%)
Eosinophilic focus	15 (30%)	9 (18%)	15 (30%)
Fibrosis, focal		1 (2%)	
Hepatodiaphragmatic nodule			2 (4%)
Mixed cell focus	2 (4%)	5 (10%)	2 (4%)
Necrosis, focal	1 (2%)		3 (6%)
Bile duct, cyst		2 (4%)	
Bile duct, hyperplasia			1 (2%)
Hepatocyte, centrilobular, hypertrophy	1 (2%)	1 (2%)	
Mesentery		(1)	(2)
Artery, inflammation, chronic		1 (100%)	
Fat, necrosis			2 (100%)
Pancreas	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Hyperkeratosis		1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
Ulcer	1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)
Ulcer	1 (2%)		
Epithelium, hyperplasia, focal		1 (2%)	1 (2%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Artery, inflammation, chronic	1 (2%)	1 (2%)	
Myocardium, degeneration	5 (10%)	3 (6%)	8 (16%)
Myocardium, mineralization			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 Lauric Acid Diethanolamine Condensate

	Vehicle Control	100 mg/kg	200 mg/kg
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Angiectasis	1 (2%)		
Hyperplasia, focal	30 (60%)	17 (34%)	24 (48%)
Hypertrophy	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal			2 (4%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	27 (54%)	28 (56%)	12 (24%)
Parathyroid gland	(40)	(42)	(43)
Cyst	1 (3%)		
Pituitary gland	(48)	(49)	(50)
Angiectasis	1 (2%)		
Pars distalis, hyperplasia, focal		1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
Follicle, hyperplasia, focal	18 (36%)	24 (48%)	36 (72%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Granuloma sperm		1 (2%)	
Preputial gland	(50)	(50)	(50)
Cyst	23 (46%)	19 (38%)	16 (32%)
Hyperplasia		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative		1 (2%)	
Bilateral, cyst			2 (4%)
Seminal vesicle	(50)	(50)	(50)
Fibrosis	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)
Hematopoietic System			
Lymph node, mesenteric	(49)	(49)	(50)
Hyperplasia, lymphoid		2 (4%)	2 (4%)
Spleen	(50)	(50)	(50)
Hematopoietic cell proliferation	6 (12%)	7 (14%)	2 (4%)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	
Thymus	(45)	(45)	(49)
Hyperplasia			1 (2%)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Integumentary System			
Skin	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
Epidermis, skin, site of application, hyperplasia	4 (8%)	45 (90%)	50 (100%)
Pinna, fibrosis, focal		1 (2%)	
Sebaceous gland, skin, site of application, hyperplasia	1 (2%)	45 (90%)	48 (96%)
Skin, site of application, hyperkeratosis	3 (6%)	45 (90%)	49 (98%)
Skin, site of application, inflammation, chronic active	1 (2%)	13 (26%)	28 (56%)
Skin, site of application, parakeratosis		1 (2%)	5 (10%)
Skin, site of application, ulcer			2 (4%)
Subcutaneous tissue, edema		1 (2%)	
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)
Thrombosis		1 (2%)	
Alveolar epithelium, hyperplasia, focal	1 (2%)	3 (6%)	2 (4%)
Mediastinum, infiltration cellular, mast cell			1 (2%)
Nose	(50)	(50)	(50)
Inflammation, suppurative		2 (4%)	
Polyp, inflammatory			2 (4%)
Special Senses System			
Eye			(3)
Degeneration			1 (33%)
Urinary System			
Kidney	(50)	(50)	(50)
Infarct		1 (2%)	
Nephropathy	28 (56%)	31 (62%)	33 (66%)
Artery, inflammation, chronic		1 (2%)	
Renal tubule, cyst	2 (4%)	2 (4%)	

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental death			1
Moribund	9	7	15
Natural deaths	4	2	5
Survivors			
Terminal sacrifice	37	40	29
Missing		1	
Animals examined microscopically	50	49	50
Alimentary System			
Intestine small, duodenum	(50)	(49)	(50)
Polyp adenomatous	1 (2%)		
Intestine small, jejunum	(50)	(49)	(50)
Liver	(50)	(49)	(50)
Hemangiosarcoma	2 (4%)	1 (2%)	
Hepatoblastoma			1 (2%)
Hepatocellular carcinoma	7 (14%)	10 (20%)	14 (28%)
Hepatocellular carcinoma, multiple	3 (6%)	3 (6%)	2 (4%)
Hepatocellular adenoma	11 (22%)	18 (37%)	14 (28%)
Hepatocellular adenoma, multiple	12 (24%)	15 (31%)	15 (30%)
Histiocytic sarcoma			2 (4%)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)
Mesentery	(7)	(10)	(4)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (25%)
Pancreas	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Salivary glands	(50)	(49)	(50)
Cardiovascular System			
Heart	(50)	(49)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)
Endocrine System			
Adrenal cortex	(50)	(49)	(50)
Adenoma	1 (2%)		
Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma malignant			1 (2%)
Pheochromocytoma benign	1 (2%)		2 (4%)
Islets, pancreatic	(50)	(49)	(50)
Adenoma	1 (2%)	1 (2%)	
Pituitary gland	(47)	(49)	(50)
Pars distalis, adenoma	9 (19%)	9 (18%)	7 (14%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(50)	(49)	(50)
Follicular cell, adenoma	4 (8%)	3 (6%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
General Body System			
None			
Genital System			
Ovary	(50)	(49)	(50)
Cystadenoma	4 (8%)	1 (2%)	2 (4%)
Granulosa cell tumor malignant		1 (2%)	
Granulosa cell tumor benign		2 (4%)	1 (2%)
Granulosa-theca tumor malignant	1 (2%)	1 (2%)	
Histiocytic sarcoma			1 (2%)
Bilateral, granulosa cell tumor benign	1 (2%)		
Uterus	(50)	(49)	(50)
Deciduoma benign		1 (2%)	
Granulosa-theca tumor malignant, metastatic, ovary	1 (2%)		
Histiocytic sarcoma			1 (2%)
Polyp stromal	2 (4%)	1 (2%)	
Schwannoma malignant		1 (2%)	1 (2%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
Lymph node	(5)	(4)	(7)
Lumbar, fibrous histiocytoma	1 (20%)		
Lumbar, histiocytic sarcoma			1 (14%)
Mediastinal, fibrous histiocytoma	1 (20%)		
Mediastinal, pheochromocytoma malignant, metastatic, adrenal medulla			1 (14%)
Popliteal, fibrous histiocytoma	1 (20%)		
Renal, fibrous histiocytoma	1 (20%)		
Renal, hemangiosarcoma		1 (25%)	
Lymph node, mandibular	(46)	(48)	(48)
Hemangiosarcoma			1 (2%)
Histiocytic sarcoma			1 (2%)
Lymph node, mesenteric	(49)	(48)	(47)
Fibrous histiocytoma	1 (2%)		
Histiocytic sarcoma			1 (2%)
Spleen	(50)	(49)	(50)
Fibrous histiocytoma		1 (2%)	
Hemangiosarcoma	2 (4%)		1 (2%)
Histiocytic sarcoma			1 (2%)
Thymus	(50)	(47)	(50)
Histiocytic sarcoma			1 (2%)
Thymoma benign			1 (2%)
Integumentary System			
Mammary gland	(49)	(49)	(50)
Carcinoma	1 (2%)		
Skin	(50)	(49)	(50)
Subcutaneous tissue, fibrosarcoma			2 (4%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Subcutaneous tissue, skin, site of application, fibrosarcoma			1 (2%)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Musculoskeletal System			
Skeletal muscle	(1)	(1)	(1)
Rhabdomyosarcoma		1 (100%)	1 (100%)
Nervous System			
Brain	(50)	(49)	(50)
Respiratory System			
Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	7 (14%)	3 (6%)	3 (6%)
Carcinoma, metastatic, harderian gland	1 (2%)	1 (2%)	
Granular cell tumor malignant, metastatic, ovary		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)	2 (4%)
Histiocytic sarcoma			2 (4%)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)
Mediastinum, hemangiosarcoma			1 (2%)
Special Senses System			
Harderian gland	(2)	(1)	(1)
Adenoma	1 (50%)		
Carcinoma	1 (50%)	1 (100%)	1 (100%)
Urinary System			
Kidney	(50)	(49)	(50)
Urinary bladder	(50)	(49)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(49)	(50)
Histiocytic sarcoma			2 (4%)
Lymphoma malignant	9 (18%)	5 (10%)	9 (18%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	44	43	45
Total primary neoplasms	90	82	85
Total animals with benign neoplasms	34	37	35
Total benign neoplasms	50	53	44
Total animals with malignant neoplasms	30	22	31
Total malignant neoplasms	40	29	41
Total animals with metastatic neoplasms	5	4	3
Total metastatic neoplasms	6	4	7

[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 Lauric Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	4 1 0	5 4 2	5 6 2	5 6 2	6 0 2	6 2 4	6 2 9	6 3 8	6 4 3	6 4 6	6 7 1	7 1 9	7 2 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 6 2	1 7 1	1 8 4	1 9 6	1 7 7	1 6 4	1 6 3	1 9 0	1 6 6	1 8 7	1 8 1	1 8 0	1 7 9	1 5 1	1 5 2	1 5 4	1 5 5	1 5 6	1 5 7	1 6 0	1 6 1	1 6 8	1 7 3	1 7 8	1 8 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma		X				X		X					X												X
Hepatocellular carcinoma, multiple																			X						
Hepatocellular adenoma		X	X															X		X			X		
Hepatocellular adenoma, multiple							X						X						X			X		X	X
Mesentery																								+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma												X					X					X		X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X																				X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma														X											
Granulosa-theca tumor malignant										X															
Bilateral, granulosa cell tumor, benign														X											

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

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 8 8	1 8 9	1 9 1	1 9 5	1 9 8	1 9 9	2 0 0	1 5 3	1 5 8	1 5 9	1 6 5	1 6 7	1 6 9	1 7 0	1 7 2	1 7 4	1 7 5	1 7 6	1 8 3	1 8 5	1 8 6	1 9 2	1 9 3	1 9 4	1 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous															X											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							2
Hepatocellular carcinoma										X											X					7
Hepatocellular carcinoma, multiple			X										X													3
Hepatocellular adenoma	X							X				X					X					X	X			1
Hepatocellular adenoma, multiple									X	X	X			X		X		X								12
Mesentery						+			+	+											+	+				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Pars distalis, adenoma					X				X		X											X			X	9
Pars distalis, adenoma, multiple				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																			X	X						4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma				X	X		X																			4
Granulosa-theca tumor malignant																										1
Bilateral, granulosa cell tumor benign																										1

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

Number of Days on Study	4 1 0	5 4 2	5 6 2	5 6 2	6 0 2	6 2 4	6 2 9	6 3 8	6 4 3	6 4 6	6 7 1	7 1 9	7 2 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 6 2	1 7 1	1 8 4	1 9 6	1 7 7	1 6 4	1 6 3	1 9 0	1 6 6	1 8 7	1 8 1	1 8 0	1 7 9	1 5 1	1 5 2	1 5 4	1 5 5	1 5 6	1 5 7	1 6 0	1 6 1	1 6 8	1 7 3	1 7 8	1 8 2
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary										X															
Polyp stromal														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Lymph node			+				+		+	+				+											
Lumbar, fibrous histiocytoma							X																		
Mediastinal, fibrous histiocytoma							X																		
Popliteal, fibrous histiocytoma							X																		
Renal, fibrous histiocytoma							X																		
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X				X														
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																		X		X			X		
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver						X		X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X					X			X	X	X	X	X								X	

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 8 8	1 8 9	1 9 1	1 9 5	1 9 8	1 9 9	2 0 0	1 5 3	1 5 8	1 5 9	1 6 5	1 6 7	1 6 9	1 7 0	1 7 2	1 7 4	1 7 5	1 7 6	1 8 3	1 8 5	1 8 6	1 9 2	1 9 3	1 9 4	1 9 7	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Polyp stromal					X																					2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																										5
Lumbar, fibrous histiocytoma																										1
Mediastinal, fibrous histiocytoma																										1
Popliteal, fibrous histiocytoma																										1
Renal, fibrous histiocytoma																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Fibrous histiocytoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Alveolar/bronchiolar carcinoma								X	X									X				X				7
Carcinoma, metastatic, harderian gland															X											1
Hepatocellular carcinoma, metastatic, liver																					X					3
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland															+				+							2
Adenoma																			X							1
Carcinoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X																									9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	4 8 1	5 7 4	6 3 8	6 3 8	6 5 1	6 5 6	6 6 6	6 6 8	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	2 2 1	2 1 9	2 0 7	2 2 5	2 2 9	2 4 6	2 4 3	2 4 7	2 3 2	2 0 1	2 0 2	2 0 9	2 1 3	2 1 6	2 1 7	2 1 8	2 2 0	2 2 2	2 2 3	2 2 4	2 3 1	2 3 3	2 3 8	2 4 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma			X																	X		X		X
Hepatocellular carcinoma, multiple				X					X															
Hepatocellular adenoma					X						X	X		X			X	X		X	X	X		
Hepatocellular adenoma, multiple							X			X		X	X		X	X							X	
Mesentery					+														+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X												
Parathyroid gland	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X								X						X	X			X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma								X																
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Granulosa cell tumor malignant																								X
Granulosa cell tumor benign															X		X							
Granulosa-theca tumor malignant																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign																								
Polyp stromal																								
Schwannoma malignant																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	24404	24408	24409	20003	20004	20005	20006	20008	21010	21011	21012	21014	21015	22606	22607	22608	23010	23404	23505	23606	23707	23909	24202	24505	25010	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma											X															1
Hepatocellular carcinoma		X						X			X				X			X	X							10
Hepatocellular carcinoma, multiple																					X					3
Hepatocellular adenoma	X		X				X				X		X							X			X	X		X	18
Hepatocellular adenoma, multiple				X	X	X		X	X						X	X					X						15
Mesentery					+	+		+	+				+		+					+	+						10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma								X								X					X		X			9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma															X			X								3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																								X		1
Granulosa cell tumor malignant																										1
Granulosa cell tumor benign																										2
Granulosa-theca tumor malignant															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Deciduoma benign											X															1
Polyp stromal																								X		1
Schwannoma malignant																				X						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	4 8 1	5 7 4	6 3 8	6 3 8	6 5 1	6 5 6	6 6 6	6 6 8	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	2 2 1	2 1 9	2 0 7	2 2 5	2 2 9	2 4 6	2 4 3	2 4 7	2 3 2	2 0 1	2 0 2	2 0 9	2 1 3	2 1 6	2 1 7	2 1 8	2 2 0	2 2 2	2 2 3	2 2 4	2 3 1	2 3 3	2 3 8	2 4 0
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																								+
Renal, hemangiosarcoma																								X
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																								
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																					
Rhabdomyosarcoma			X																					
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																		
Spinal cord						+																		
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X		
Alveolar/bronchiolar carcinoma																X					X			
Carcinoma, metastatic, harderian gland																								
Granular cell tumor malignant, metastatic, ovary																								X
Hepatocellular carcinoma, metastatic, liver				X					X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant								X																X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 100 mg/kg

Number of Days on Study	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	24404	24408	24409	20003	20004	20005	20006	20008	21010	21011	21012	21014	21015	22026	22027	22028	23020	23034	23035	23036	23037	23039	24202	24504	25050	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node				+																+					+	4	
Renal, hemangiosarcoma																										1	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Fibrous histiocytoma		X																								1	
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Skeletal muscle																										1	
Rhabdomyosarcoma																										1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Peripheral nerve																										1	
Spinal cord																										1	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Alveolar/bronchiolar adenoma																X										2	
Alveolar/bronchiolar carcinoma					X																					3	
Carcinoma, metastatic, harderian gland																							X			1	
Granular cell tumor malignant, metastatic, ovary																										1	
Hepatocellular carcinoma, metastatic, liver																										2	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Special Senses System																											
Harderian gland																							+			1	
Carcinoma																							X			1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymphoma malignant				X															X						X	5	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	26 4	27 4	27 6	27 7	28 2	28 5	29 1	29 5	29 6	29 8	29 9	30 0	25 1	26 0	26 2	26 5	26 7	26 8	27 0	27 9	28 0	28 3	28 4	28 7	29 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma								X																		1
Hepatocellular carcinoma				X			X								X	X			X					X		14
Hepatocellular carcinoma, multiple												X	X													2
Hepatocellular adenoma	X							X										X		X				X		14
Hepatocellular adenoma, multiple			X	X		X	X			X	X			X			X		X		X				X	15
Histiocytic sarcoma																										2
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Mesentery								+						+												4
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																				X		X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X												X		X	X				X					7
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	0 8 4	4 1 4	4 5 7	4 7 6	5 1 7	5 2 3	5 3 9	5 8 3	5 9 6	6 1 5	6 1 6	6 1 7	6 2 5	6 2 5	6 4 6	6 5 0	6 5 3	6 8 0	7 2 0	7 2 0	7 2 8	7 3 6	7 3 6	7 3 6
Carcass ID Number	2 7 2	2 7 8	2 5 3	2 6 9	2 8 6	2 5 9	2 8 9	2 8 1	2 7 3	2 9 3	2 9 7	2 6 6	2 7 1	2 8 8	2 9 2	2 6 1	2 5 8	2 9 0	2 5 4	2 5 5	2 7 5	2 5 2	2 5 6	2 5 7	2 6 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																									
Histiocytic sarcoma																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Schwannoma malignant																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+					+	+								+				
Lumbar, histiocytic sarcoma																					X				
Mediastinal, pheochromocytoma malignant, metastatic, adrenal medulla							X																		
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Histiocytic sarcoma																					X				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Histiocytic sarcoma																					X				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Thymoma benign																			X						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma														X			X								
Subcutaneous tissue, site of application, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Rhabdomyosarcoma																				X					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	26 4	27 4	27 6	27 7	28 2	28 5	29 1	29 5	29 6	29 8	29 9	30 0	25 1	26 0	26 2	26 5	26 7	26 8	27 0	27 9	28 0	28 3	28 4	28 7	29 4	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																X	X									2
Granulosa cell tumor benign			X																							1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Schwannoma malignant								X																		1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+									+			7
Lumbar, histiocytic sarcoma																										1
Mediastinal, pheochromocytoma malignant, metastatic, adrenal medulla																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, site of application, fibrosarcoma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	0 8 4	4 1 4	4 5 7	4 7 6	5 1 7	5 2 3	5 3 9	5 8 3	5 9 6	6 1 5	6 1 6	6 1 7	6 2 5	6 2 5	6 4 6	6 5 0	6 5 3	6 8 0	7 2 0	7 2 0	7 2 8	7 3 6	7 3 6	7 3 6
Carcass ID Number	2 7 2	2 7 8	2 5 3	2 6 9	2 8 6	2 5 9	2 8 9	2 8 1	2 7 3	2 9 3	2 9 7	2 6 6	2 7 1	2 8 8	2 9 2	2 6 1	2 5 8	2 9 0	2 5 4	2 5 5	2 7 5	2 5 2	2 5 6	2 5 7	2 6 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									X
Hepatocellular carcinoma, metastatic, liver										X	X														
Histiocytic sarcoma									X												X				
Pheochromocytoma malignant, metastatic, adrenal medulla							X																		
Mediastinum, hemangiosarcoma						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X												X				
Lymphoma malignant			X									X	X											X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Lauric Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	26404	26744	27476	27767	28202	28485	29291	29595	29906	29988	30299	30300	30551	30660	30662	30765	30767	30788	30970	30979	31080	31083	31284	31287	31294	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											1
Alveolar/bronchiolar carcinoma										X																X	3
Hepatocellular carcinoma, metastatic, liver																											2
Histiocytic sarcoma																											2
Pheochromocytoma malignant, metastatic, adrenal medulla																											1
Mediastinum, hemangiosarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland																							+				1
Carcinoma																							X				1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											2
Lymphoma malignant							X					X		X							X		X				9

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

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate[a]	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted rate[b]	2.2%	0.0%	7.3%
Terminal rate[c]	0/37 (0%)	0/40 (0%)	2/29 (7%)
First incidence (days)	638	—[e]	539
Poly-3 test[d]	P=0.172	P=0.497N	P=0.272
Liver: Hepatocellular Adenoma			
Overall rate	23/50 (46%)	32/49 (65%)	29/50 (58%)
Adjusted rate	49.5%	68.8%	65.8%
Terminal rate	19/37 (51%)	30/40 (75%)	19/29 (66%)
First incidence (days)	542	651	517
Poly-3 test	P=0.059	P=0.041	P=0.081
Liver: Hepatocellular Carcinoma			
Overall rate	10/50 (20%)	13/49 (27%)	16/50 (32%)
Adjusted rate	21.6%	27.9%	38.2%
Terminal rate	6/37 (16%)	10/40 (25%)	11/29 (38%)
First incidence (days)	542	638	615
Poly-3 test	P=0.059	P=0.324	P=0.068
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	28/50 (56%)	40/49 (82%)	36/50 (72%)
Adjusted rate	59.3%	84.7%	80.3%
Terminal rate	22/37 (60%)	35/40 (88%)	24/29 (83%)
First incidence (days)	542	638	517
Poly-3 test	P=0.009	P=0.004	P=0.019
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	10/50 (20%)	13/49 (27%)	17/50 (34%)
Adjusted rate	21.6%	27.9%	40.6%
Terminal rate	6/37 (16%)	10/40 (25%)	12/29 (41%)
First incidence (days)	542	638	615
Poly-3 test	P=0.036	P=0.324	P=0.042
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	28/50 (56%)	40/49 (82%)	36/50 (72%)
Adjusted rate	59.3%	84.7%	80.3%
Terminal rate	22/37 (60%)	35/40 (88%)	24/29 (83%)
First incidence (days)	542	638	517
Poly-3 test	P=0.009	P=0.004	P=0.019
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	7/50 (14%)	3/49 (6%)	3/50 (6%)
Adjusted rate	15.6%	6.5%	7.4%
Terminal rate	7/37 (19%)	3/40 (8%)	3/29 (10%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Poly-3 test	P=0.132N	P=0.147N	P=0.201N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	8/50 (16%)	5/49 (10%)	4/50 (8%)
Adjusted rate	17.8%	10.9%	9.9%
Terminal rate	8/37 (22%)	5/40 (13%)	4/29 (14%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Poly-3 test	P=0.174N	P=0.260N	P=0.229N
Ovary: Cystadenoma			
Overall rate	4/50 (8%)	1/49 (2%)	2/50 (4%)
Adjusted rate	8.9%	2.2%	4.9%
Terminal rate	4/37 (11%)	1/40 (3%)	2/29 (7%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Poly-3 test	P=0.266N	P=0.172N	P=0.385N
Ovary: Benign or Malignant Granulosa Cell Tumor			
Overall rate	1/50 (2%)	3/49 (6%)	1/50 (2%)
Adjusted rate	2.2%	6.5%	2.5%
Terminal rate	1/37 (3%)	3/40 (8%)	1/29 (3%)
First incidence (days)	736 (T)	736 (T)	736 (T)
Poly-3 test	P=0.564	P=0.314	P=0.737
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	10/47 (21%)	9/49 (18%)	7/50 (14%)
Adjusted rate	23.8%	19.5%	17.0%
Terminal rate	9/34 (27%)	8/40 (20%)	5/29 (17%)
First incidence (days)	719	651	583
Poly-3 test	P=0.263N	P=0.405N	P=0.305N
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rate	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	7.3%
Terminal rate	0/37 (0%)	0/40 (0%)	1/29 (3%)
First incidence (days)	—	—	625
Poly-3 test	P=0.035	—[f]	P=0.104
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	4/50 (8%)	3/49 (6%)	0/50 (0%)
Adjusted rate	8.8%	6.5%	0.0%
Terminal rate	3/37 (8%)	2/40 (5%)	0/29 (0%)
First incidence (days)	562	668	—
Poly-3 test	P=0.066N	P=0.491N	P=0.076N
All Organs: Hemangiosarcoma			
Overall rate	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rate	6.6%	4.4%	4.9%
Terminal rate	1/37 (3%)	2/40 (5%)	1/29 (3%)
First incidence (days)	629	736 (T)	523
Poly-3 test	P=0.450N	P=0.496N	P=0.546N

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

	Vehicle Control	100 mg/kg	200 mg/kg
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rate	6.6%	4.4%	4.9%
Terminal rate	1/37 (3%)	2/40 (5%)	1/29 (3%)
First incidence (days)	629	736 (T)	523
Poly-3 test	P=0.450N	P=0.496N	P=0.546N
All Organs: Malignant Lymphoma			
Overall rate	9/50 (18%)	5/49 (10%)	9/50 (18%)
Adjusted rate	19.6%	10.8%	21.4%
Terminal rate	5/37 (14%)	4/40 (10%)	6/29 (21%)
First incidence (days)	562	668	457
Poly-3 test	P=0.501	P=0.188N	P=0.523
All Organs: Benign Neoplasms			
Overall rate	34/50 (68%)	37/49 (76%)	35/50 (70%)
Adjusted rate	72.5%	79.2%	78.0%
Terminal rate	28/37 (76%)	34/40 (85%)	22/29 (76%)
First incidence (days)	542	651	517
Poly-3 test	P=0.300	P=0.299	P=0.352
All Organs: Malignant Neoplasms			
Overall rate	30/50 (60%)	22/49 (45%)	31/50 (62%)
Adjusted rate	62.3%	46.9%	67.5%
Terminal rate	20/37 (54%)	18/40 (45%)	17/29 (59%)
First incidence (days)	542	638	457
Poly-3 test	P=0.361	P=0.094N	P=0.376
All Organs: Benign or Malignant Neoplasms			
Overall rate	44/50 (88%)	43/49 (88%)	45/50 (90%)
Adjusted rate	90.3%	90.6%	94.8%
Terminal rate	33/37 (89%)	37/40 (93%)	27/29 (93%)
First incidence (days)	542	638	457
Poly-3 test	P=0.258	P=0.623	P=0.317

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

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

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

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Accidental death			1
Moribund	9	7	15
Natural deaths	4	2	5
Survivors			
Terminal sacrifice	37	40	29
Missing		1	
Animals examined microscopically	50	49	50
Alimentary System			
Esophagus	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)		
Intestine small, duodenum	(50)	(49)	(50)
Hyperplasia		1 (2%)	
Ulcer	2 (4%)		
Liver	(50)	(49)	(50)
Angiectasis			1 (2%)
Clear cell focus	2 (4%)	2 (4%)	1 (2%)
Degeneration, fatty, focal		2 (4%)	
Eosinophilic focus	15 (30%)	20 (41%)	23 (46%)
Hematopoietic cell proliferation		1 (2%)	
Hepatodiaphragmatic nodule			1 (2%)
Infarct	1 (2%)		
Mixed cell focus			2 (4%)
Necrosis, focal		2 (4%)	
Bile duct, cyst			1 (2%)
Mesentery	(7)	(10)	(4)
Fat, necrosis	7 (100%)	10 (100%)	3 (75%)
Pancreas	(50)	(49)	(50)
Infiltration cellular, lymphocyte		1 (2%)	
Inflammation, chronic	1 (2%)		
Acinus, atrophy	1 (2%)	2 (4%)	
Stomach, forestomach	(50)	(49)	(50)
Ulcer	3 (6%)		
Epithelium, hyperkeratosis	2 (4%)		
Stomach, glandular	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
Ulcer		1 (2%)	1 (2%)
Cardiovascular System			
Heart	(50)	(49)	(50)
Artery, inflammation, chronic			1 (2%)
Atrium, thrombosis	1 (2%)		1 (2%)
Myocardium, degeneration	5 (10%)	10 (20%)	5 (10%)
Myocardium, mineralization, focal			1 (2%)
Ventricle, inflammation, chronic, focal	1 (2%)		

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Endocrine System			
Adrenal cortex	(50)	(49)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Hyperplasia, focal	1 (2%)	4 (8%)	
Necrosis, acute			1 (2%)
Adrenal medulla	(50)	(49)	(50)
Hyperplasia, focal	2 (4%)	2 (4%)	2 (4%)
Necrosis			1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Hyperplasia	2 (4%)	9 (18%)	6 (12%)
Pituitary gland	(47)	(49)	(50)
Pars distalis, angiectasis, focal		1 (2%)	
Pars distalis, hyperplasia, focal	11 (23%)	6 (12%)	11 (22%)
Pars distalis, necrosis, focal			1 (2%)
Thyroid gland	(50)	(49)	(50)
Inflammation, chronic		1 (2%)	
C-cell, hyperplasia		2 (4%)	
Follicle, hyperplasia, diffuse		1 (2%)	
Follicle, hyperplasia, focal	38 (76%)	34 (69%)	36 (72%)
General Body System			
None			
Genital System			
Clitoral gland	(49)	(47)	(49)
Cyst	1 (2%)	1 (2%)	1 (2%)
Ovary	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	
Cyst	6 (12%)	9 (18%)	8 (16%)
Thrombosis	1 (2%)		1 (2%)
Uterus	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	2 (4%)
Inflammation, granulomatous			1 (2%)
Endometrium, hyperplasia, cystic	38 (76%)	46 (94%)	39 (78%)
Myometrium, hyperplasia	1 (2%)		
Hematopoietic System			
Lymph node	(5)	(4)	(7)
Mediastinal, hyperplasia, lymphoid	1 (20%)	1 (25%)	
Renal, hyperplasia, lymphoid	1 (20%)	1 (25%)	
Lymph node, mandibular	(46)	(48)	(48)
Hyperplasia, lymphoid			1 (2%)
Lymph node, mesenteric	(49)	(48)	(47)
Angiectasis		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
Spleen	(50)	(49)	(50)
Hematopoietic cell proliferation	7 (14%)	6 (12%)	9 (18%)
Hyperplasia, lymphoid	6 (12%)	3 (6%)	1 (2%)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System (continued)			
Thymus	(50)	(47)	(50)
Ectopic parathyroid gland	1 (2%)		
Hemorrhage			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Integumentary System			
Skin	(50)	(49)	(50)
Epidermis, skin, site of application, hyperplasia		42 (86%)	50 (100%)
Sebaceous gland, skin, site of application, hyperplasia		43 (88%)	45 (90%)
Skin, site of application, hyperkeratosis	4 (8%)	41 (84%)	48 (96%)
Skin, site of application, inflammation, chronic active		24 (49%)	40 (80%)
Skin, site of application, parakeratosis		3 (6%)	9 (18%)
Skin, site of application, ulcer			3 (6%)
Subcutaneous tissue, edema			1 (2%)
Musculoskeletal System			
Bone	(50)	(49)	(50)
Fibrosis	1 (2%)	3 (6%)	
Fibrous osteodystrophy	1 (2%)		
Nervous System			
Brain	(50)	(49)	(50)
Meninges, infiltration cellular, mixed cell		1 (2%)	
Spinal cord		(1)	
Axon, nerve, degeneration		1 (100%)	
Respiratory System			
Lung	(50)	(49)	(50)
Hemorrhage, focal	1 (2%)		1 (2%)
Inflammation,granulomatous			1 (2%)
Thrombosis			1 (2%)
Alveolar epithelium, hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Mediastinum, inflammation, chronic active	1 (2%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(49)	(50)
Infarct	1 (2%)		
Nephropathy	19 (38%)	30 (61%)	16 (32%)
Urinary bladder	(50)	(49)	(50)
Artery, inflammation, chronic		1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1988). Lauric 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 lauric 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). Lauric acid diethanolamine condensate was supplied as a coded aliquot by Radian Corporation. The high dose of lauric 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 lauric acid diethanolamine condensate continued for 4 hours, at which time the medium plus lauric 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 with freshly prepared S9 from the livers of Aroclor 1254-induced male Fischer 344 rats.

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

condensate to be considered positive, i.e., capable of inducing TFT resistance. A single significant response would lead to a call of "questionable," and the absence of both a trend and peak response results in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987) and Loveday *et al.* (1990). Lauric acid diethanolamine condensate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of lauric acid diethanolamine condensate; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with lauric acid diethanolamine condensate in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing lauric acid diethanolamine condensate was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with lauric acid diethanolamine condensate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no lauric acid diethanolamine condensate. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

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

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with lauric acid diethanolamine condensate for 8 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with lauric acid diethanolamine condensate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations

included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 14-week dermal study, peripheral blood samples were obtained from male and female mice, and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Lauric acid diethanolamine condensate (0.3 to 1,000 μg/plate) was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation (Zeiger *et al.*, 1988; Table E1). In addition, no increase in the frequency of mutant colonies of L5178Y mouse lymphoma cells was observed after exposure to lauric acid diethanolamine condensate, with or without S9 (Table E2). In cytogenetic tests with cultured CHO cells, lauric acid diethanolamine condensate was shown to induce SCEs both in the presence and absence of S9 (Loveday *et al.*, 1990; Table E3). However, the number of Abs was not increased in cultured CHO cells exposed to similar concentrations of lauric acid diethanolamine condensate with or without S9 (Loveday *et al.*, 1990; Table E4). *In vivo*, no increase in the frequency of micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male or female mice treated dermally with lauric acid diethanolamine condensate for 14 weeks (Table E5).

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

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+hamster S9 10%	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 10%	+rat S9 30%
TA100	0.0	105 ± 6.5	157 ± 4.5	179 ± 5.2	122 ± 8.4	150 ± 10.1	172 ± 13.0	106 ± 3.8	168 ± 3.3	168 ± 8.5
	0.3			148 ± 10.4						
	1.0		123 ± 9.4	150 ± 17.4			158 ± 9.6			167 ± 3.2
	3.0	121 ± 5.5	128 ± 12.7	145 ± 7.3		144 ± 3.5	169 ± 13.9		171 ± 8.1	180 ± 9.0
	10.0	127 ± 7.8	139 ± 8.0	149 ± 7.4	123 ± 11.3	137 ± 13.6	159 ± 14.0	103 ± 2.4	162 ± 6.9	157 ± 4.7
	33.0	99 ± 3.0[c]	16 ± 16.0[c]	136 ± 10.5	112 ± 1.8	154 ± 2.6	178 ± 7.2	98 ± 6.4	184 ± 7.4	161 ± 3.0
	66.0		Toxic							
	100.0	Toxic			115 ± 10.3	163 ± 1.2	169 ± 16.1	110 ± 5.7	147 ± 17.3	155 ± 11.3
	166.0					108 ± 13.6[c]			106 ± 15.7[c]	
	333.0	Toxic			31 ± 3.5[c]			26 ± 5.0[c]		
	1,000.0				Toxic			Toxic		
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		647 ± 15.5	400 ± 4.3	475 ± 35.9	1,599 ± 57.7	1,555 ± 38.8	1,814 ± 40.2	541 ± 7.2	513 ± 2.6	509 ± 6.0

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

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+hamster S9 10%	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 10%	+rat S9 30%
TA1535	0.0	27 ± 1.5	29 ± 1.2	19 ± 5.5	8 ± 2.1	12 ± 2.0	11 ± 3.2	8 ± 1.5	7 ± 2.0	11 ± 4.3
	0.3			20 ± 4.1						
	1.0		22 ± 1.7	20 ± 3.5			10 ± 1.9			14 ± 1.0
	3.0	26 ± 0.6	24 ± 1.0	13 ± 3.7		10 ± 1.2	10 ± 1.9		11 ± 0.6	11 ± 2.2
	10.0	26 ± 0.6	19 ± 2.3	15 ± 3.6	6 ± 0.7	7 ± 2.0	6 ± 1.5	10 ± 0.7	8 ± 1.2	10 ± 2.2
	33.0	23 ± 3.7	17 ± 3.5	16 ± 1.9	5 ± 0.3	12 ± 2.9	8 ± 0.9	10 ± 0.3	6 ± 0.6	14 ± 0.9
	66.0		0 ± 0.0[c]							
	100.0	Toxic			5 ± 0.3	8 ± 1.7	8 ± 3.7	10 ± 2.0	6 ± 2.4	14 ± 2.8
	166.0					11 ± 0.9			7 ± 3.0	
	333.0	Toxic			2 ± 1.0[c]			5 ± 0.7[c]		
	1,000.0				Toxic			Toxic		
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		666 ± 20.3	562 ± 14.7	413 ± 13.2	518 ± 30.8	642 ± 21.8	581 ± 24.0	340 ± 9.8	166 ± 12.5	198 ± 31.6

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

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+hamster S9 10%	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 10%	+rat S9 30%
TA97	0.0	175 ± 15.0	167 ± 1.7	140 ± 3.8	159 ± 8.2	183 ± 1.9	174 ± 7.5	195 ± 10.4	194 ± 8.7	188 ± 9.0
	0.3			160 ± 6.7			179 ± 3.2			199 ± 5.9
	1.0		153 ± 5.5	157 ± 5.3		185 ± 5.5	183 ± 9.8		182 ± 12.9	191 ± 19.9
	3.0	164 ± 7.7	156 ± 4.9	159 ± 5.4	160 ± 4.5	179 ± 8.1	178 ± 8.8	216 ± 2.3	174 ± 6.6	195 ± 6.5
	10.0	178 ± 15.9	159 ± 7.2	162 ± 6.8	140 ± 6.7	186 ± 7.5	189 ± 8.8	202 ± 7.1	196 ± 20.5	200 ± 14.2
	33.0	160 ± 5.5[c]	33 ± 23.1[c]	138 ± 13.8	174 ± 8.5	182 ± 10.1	193 ± 10.0	194 ± 19.5	158 ± 2.0	142 ± 12.5
	66.0		Toxic			159 ± 9.2[c]			73 ± 10.7[c]	
	100.0	Toxic			18 ± 7.0[c]			31 ± 11.6[c]		
	333.0	Toxic			Toxic			Toxic		
	1,000.0									
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,837 ± 73.6	1,205 ±72.3	1,420 ± 8.1	1,885 ± 34.6	1,406 ± 43.1	1,351 ± 54.5	975 ± 1.8	883 ± 26.9	442 ± 11.2

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

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+hamster S9 10%	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 10%	+rat S9 30%
TA98	0.0	22 ± 1.5	26 ± 1.0	31 ± 3.2	31 ± 3.0	39 ± 4.5	30 ± 3.7	30 ± 1.7	37 ± 4.0	37 ± 4.3
	0.3			25 ± 2.6						
	1.0		24 ± 2.3	18 ± 1.8			33 ± 4.0			30 ± 2.2
	3.0	21 ± 2.3	22 ± 2.7	21 ± 5.4		36 ± 6.0	29 ± 1.5		23 ± 8.9	33 ± 2.8
	10.0	16 ± 0.3	22 ± 0.9	23 ± 5.7	29 ± 0.9	34 ± 2.8	32 ± 1.9	25 ± 0.6	45 ± 4.5	34 ± 7.8
	33.0	20 ± 0.9[c]	12 ± 1.5[c]	20 ± 2.0	25 ± 3.8	30 ± 1.5	30 ± 5.0	24 ± 5.1	24 ± 2.3	26 ± 2.9
	66.0		0 ± 0.0[c]							
	100.0	Toxic			19 ± 1.0	28 ± 3.4	32 ± 6.9	21 ± 1.9	30 ± 1.5	36 ± 3.3
	166.0					18 ± 1.8[c]			26 ± 1.5[c]	
	333.0	Toxic			19 ± 0.9[c]			11 ± 1.5[c]		
	1,000.0				Toxic			Toxic		
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,437 ± 18.1	1,746 ± 18.6	1,653 ± 83.6	1,603 ± 28.0	820 ± 77.4	926 ± 48.5	313 ± 10.3	225 ± 12.0	169 ± 17.1

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Zeiger *et al.* (1988).
[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 Lauric Acid Diethanolamine Condensate[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Ethanol[c]		59	98	72	40	
		73	113	53	24	
		64	88	83	43	36
Methyl methanesulfonate[d]						
	5	93	116	178	64	
		76	83	379	167	
		60	72	433	240	157*
Lauric acid diethanolamine condensate						
	2.5	47	94	38	27	
		34	69	27	26	
		50	97	46	31	28
	5	45	67	65	48	
		63	112	55	29	
		68	112	86	42	40
	10	93	149	91	33	
		88	142	45	17	
		90	132	74	27	26
	20	80	94	61	25	
		88	101	62	23	
		101	142	67	22	24
	30	83	119	53	21	
		52	13	89	57	
		88	100	54	21	33
	40	54	12	60	37	
		49	24	86	59	
		44	29	44	33	43
	50	Lethal				
		Lethal				

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

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9 (continued)						
Trial 2						
Ethanol		111	97	217	65	
		115	130	292	85	
		117	112	141	40	
		106	60	183	58	62
Methyl methanesulfonate						
	5	98	59	924	315	
		39	28	847	721	
		77	43	900	390	475*
Lauric acid diethanolamine condensate						
	5	118	77	185	52	
		105	80	204	65	
		118	94	194	55	57
	10	47	36	131	94	
		111	66	206	62	
		115	91	137	40	65
	20	119	55	169	47	
		115	50	144	42	
		108	29	296	91	60
	30	Lethal				
		Lethal				

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

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Ethanol		73	98	121	55	
		81	103	106	44	
		69	99	137	66	
		88	100	113	43	52
Methyl cholanthrene[d]	2.5	79	48	546	231	
		102	76	474	155	
		70	56	365	175	187*
Lauric acid diethanolamine condensate						
	5	91	84	143	52	
		91	75	145	53	
		76	68	132	58	55
	10	95	94	147	51	
		81	79	169	69	60
	20	98	57	157	53	
		106	78	174	55	
		85	74	131	51	53
	30	77	65	114	50	
		86	65	170	66	
		97	61	196	67	61
	40	68	29	152	74	
		93	64	124	45	
		80	43	107	45	54
	50	63	8	105	56	
		101	21	205	68	62
	60	Lethal				
		Lethal				
		Lethal				

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

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 2						
Ethanol		110	98	144	44	
		114	102	121	36	40
Methyl cholanthrene	2.5	103	38	942	305	
		88	37	741	281	293*
Lauric acid diethanolamine condensate						
	5	107	97	164	51	
		104	98	141	45	
		81	59	149	61	53
	10	115	87	171	50	
		114	66	162	47	49
	20	112	54	147	44	
		89	61	154	58	51
	30	96	41	146	51	
		90	13	86	32	
		117	33	144	41	41
	40	Lethal				
		Lethal				
		Lethal				

* 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

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

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
S9								
Trial 1								
Summary: Positive								
Solvent control		50	1,049	342	0.32	6.8	26.0	
Mitomycin-C[c]	0.002	50	1,041	567	0.54	11.3	26.0	67.06
	0.010	10	208	243	1.16	24.3	26.0	258.34
Lauric acid diethanolamine condensate								
	2.49	50	1,042	427	0.40	8.5	26.0	25.69*
	4.97	50	1,029	461	0.44	9.2	26.0	37.41*
	14.90	50	1,037	467	0.45	9.3	26.0	38.13*
	49.70	0						
					P≤0.001[d]			
Trial 2								
Summary: Weakly positive								
Solvent control		50	1,044	348	0.33	7.0	26.0	
Mitomycin-C	0.002	50	1,028	722	0.70	14.4	26.0	110.7
	0.010	10	208	420	2.01	42.0	26.0	505.78
Lauric acid diethanolamine condensate								
	5.0	50	1,044	403	0.38	8.1	26.0	15.80
	10.0	50	1,046	398	0.38	8.0	26.0	14.15
	15.0	50	1,041	365	0.35	7.3	26.0	5.19
	20.0	50	1,043	443	0.42	8.9	26.0	27.42*
	30.0	0						
					P=0.012			

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Lauric Acid Diethanolamine Condensate

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Negative								
Solvent control		50	1,023	457	0.44	9.1	26.0	
Cyclophosphamide[c]	0.50	50	1,034	535	0.51	10.7	26.0	15.82
	2.50	10	208	224	1.07	22.4	26.0	141.07
Lauric acid diethanolamine condensate								
	2.50	50	1,030	477	0.46	9.5	26.0	3.67
	8.35	50	1,026	455	0.44	9.1	26.0	0.73
	25.00	50	1,041	435	0.41	8.7	26.0	6.46
	83.50	0						
					P=0.874			
Trial 2								
Summary: Positive								
Solvent control		50	1,034	566	0.54	11.3	26.0	
Cyclophosphamide	0.75	50	1,032	728	0.70	14.6	26.0	28.87
	2.50	20	414	520	1.25	26.0	26.0	129.46
Lauric acid diethanolamine condensate								
	10.0	50	1,029	693	0.67	13.1	26.0	23.03*
	15.0	50	1,030	689	0.66	13.8	26.0	22.21*
	20.0	50	1,031	702	0.68	14.0	26.0	24.39*
	30.0	0						
					P≤0.001			

* Positive response (≥20% increase over solvent control)
[a] Study was performed at Bioassay Systems, Corp. The detailed protocol is presented by Galloway *et al.* (1987) and the data by Loveday *et al.* (1990). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Positive control
[d] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

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

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/Cell	Cells with Aberrations (%)
-S9					
Harvest time: 10 hours					
Summary: Negative					
Solvent control		200	7	0.04	2.5
Mitomycin-C[b]	1	200	33	0.17	15.5
	5	50	53	1.06	58.0
Lauric acid diethanolamine condensate					
	4.99	200	9	0.05	4.0
	15.00	200	3	0.02	1.5
	49.90	200	1	0.01	0.5
	100.00	0			
					P=0.969[c]
+S9					
Harvest time: 12 hours					
Summary: Negative					
Solvent control		200	10	0.05	4.0
Cyclophosphamide[b]	50	50	119	2.30	72.0
Lauric acid diethanolamine condensate					
	1.50	200	9	0.05	3.5
	4.99	200	14	0.07	5.0
	15.00	200	9	0.05	3.5
	30.00	0			
					P=0.494

[a] Study was performed at Bioassay Systems, Corp. The detailed protocol is presented by Galloway *et al*. (1987). These data are published by Loveday *et al*. (1990).
[b] Positive control
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Dermal Application of Lauric Acid Diethanolamine Condensate for 14 Weeks[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/1,000 NCEs[b]
Male			
Ethanol[c]		5	2.1 ± 0.1
Lauric acid diethanolamine condensate			
	50	5	1.2 ± 0.3
	100	5	2.8 ± 0.4
	200	5	2.3 ± 0.6
	400	5	3.1 ± 0.3
	800	5	2.5 ± 0.4
			P=0.096[d]
Female			
Ethanol		5	1.8 ± 0.3
Lauric acid diethanolamine condensate			
	50	5	1.4 ± 0.3
	100	5	2.3 ± 0.4
	200	5	2.1 ± 0.2
	400	5	2.2 ± 0.4
	800	5	2.3 ± 0.3
			P=0.149

[a] Study was performed at Environmental Health Research and Testing, Inc. Two thousand normochromatic erythrocytes were scored per animal for frequency of micronuclei. NCE=normochromatic erythrocyte
[b] Mean ± standard error
[c] Vehicle control
[d] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

APPENDIX F
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male						
Hematology						
n						
Day 4	9	9	9	9	9	9
Day 24	10	10	10	10	10	10
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 4	46.6 ± 0.5	47.9 ± 0.5	47.8 ± 0.8	46.9 ± 0.2	47.2 ± 0.6	46.2 ± 0.4
Day 24	51.5 ± 0.4	51.5 ± 0.4	50.8 ± 0.5	52.8 ± 0.5	52.6 ± 0.5	51.9 ± 0.7
Week 14	48.7 ± 0.9	48.5 ± 0.6	48.8 ± 0.4	48.4 ± 0.5	48.3 ± 0.4	48.4 ± 0.8
Hemoglobin (g/dL)						
Day 4	15.5 ± 0.2	15.9 ± 0.1	15.9 ± 0.2	15.6 ± 0.1	15.6 ± 0.2	15.4 ± 0.1
Day 24	17.6 ± 0.1	17.6 ± 0.1	17.5 ± 0.1	17.8 ± 0.1	17.8 ± 0.1	17.5 ± 0.2
Week 14	16.4 ± 0.2	16.7 ± 0.2	16.7 ± 0.1	16.5 ± 0.2	16.5 ± 0.1	16.7 ± 0.2
Erythrocytes ($10^6/\mu L$)						
Day 4	7.42 ± 0.09	7.67 ± 0.07	7.65 ± 0.14	7.49 ± 0.03	7.57 ± 0.08	7.40 ± 0.05
Day 24	8.70 ± 0.07	8.66 ± 0.09	8.56 ± 0.09	8.89 ± 0.08	8.86 ± 0.09	8.67 ± 0.10
Week 14	8.93 ± 0.17	8.95 ± 0.12	9.05 ± 0.08	8.98 ± 0.09	8.93 ± 0.09	8.99 ± 0.15
Reticulocytes ($10^6/\mu L$)						
Day 4	0.18 ± 0.02	0.29 ± 0.04	0.25 ± 0.03	0.21 ± 0.03	0.27 ± 0.04	0.23 ± 0.02
Day 24	0.20 ± 0.02	0.22 ± 0.02	0.22 ± 0.02	0.23 ± 0.03	0.20 ± 0.02	0.24 ± 0.01
Week 14	0.20 ± 0.02	0.17 ± 0.01	0.21 ± 0.01	0.22 ± 0.02	0.20 ± 0.01	0.26 ± 0.02*
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.06 ± 0.02	0.12 ± 0.04	0.08 ± 0.02	0.12 ± 0.04	0.09 ± 0.02	0.08 ± 0.04
Day 24	0.03 ± 0.02	0.05 ± 0.02	0.07 ± 0.02	0.05 ± 0.02	0.02 ± 0.01	0.06 ± 0.02
Week 14	0.03 ± 0.02	0.02 ± 0.02	0.03 ± 0.02	0.02 ± 0.01	0.03 ± 0.02	0.06 ± 0.02
Mean cell volume (fL)						
Day 4	62.8 ± 0.2	62.5 ± 0.3	62.5 ± 0.4	62.6 ± 0.2	62.4 ± 0.2	62.4 ± 0.3
Day 24	59.2 ± 0.3	59.5 ± 0.3	59.3 ± 0.3	59.4 ± 0.3	59.3 ± 0.2	59.9 ± 0.3
Week 14	54.5 ± 0.2	54.2 ± 0.2	54.0 ± 0.2	53.9 ± 0.3	54.1 ± 0.3	53.9 ± 0.2
Mean cell hemoglobin (pg)						
Day 4	20.9 ± 0.2	20.7 ± 0.1	20.8 ± 0.2	20.8 ± 0.1	20.6 ± 0.1	20.9 ± 0.1
Day 24	20.2 ± 0.1	20.4 ± 0.2	20.4 ± 0.2	20.0 ± 0.1	20.1 ± 0.1	20.2 ± 0.1
Week 14	18.4 ± 0.1	18.7 ± 0.1	18.4 ± 0.1	18.4 ± 0.1	18.5 ± 0.1	18.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 4	33.3 ± 0.2	33.2 ± 0.2	33.2 ± 0.3	33.2 ± 0.2	33.0 ± 0.2	33.4 ± 0.1
Day 24	34.2 ± 0.2	34.3 ± 0.3	34.4 ± 0.3	33.7 ± 0.2	33.9 ± 0.2	33.8 ± 0.3
Week 14	33.8 ± 0.2	34.4 ± 0.2	34.2 ± 0.2	34.2 ± 0.2	34.1 ± 0.2	34.5 ± 0.3
Platelets ($10^3/\mu L$)						
Day 4	910.6 ± 42.7	1,010.4 ± 15.6	990.1 ± 25.2	944.0 ± 17.8	980.6 ± 23.5	968.2 ± 14.4
Day 24	808.7 ± 9.6	817.2 ± 21.3	784.0 ± 15.7	808.3 ± 14.0	836.1 ± 19.7	823.6 ± 13.0
Week 14	722.9 ± 12.6	706.2 ± 10.7	710.8 ± 16.4	756.6 ± 29.2	708.8 ± 9.9	703.9 ± 32.5
Leukocytes ($10^3/\mu L$)						
Day 4	7.26 ± 0.34	9.59 ± 0.82	8.54 ± 0.74	8.32 ± 0.89	9.09 ± 0.82	7.80 ± 0.34
Day 24	9.18 ± 0.37	9.25 ± 0.47	10.08 ± 0.47	9.83 ± 0.57	9.91 ± 0.37	10.62 ± 0.41
Week 14	9.49 ± 0.53	8.31 ± 0.34	9.32 ± 0.47	9.13 ± 0.47	8.93 ± 0.54	10.59 ± 0.47
Segmented neutrophils ($10^3/\mu L$)						
Day 4	0.86 ± 0.08	0.97 ± 0.10	0.86 ± 0.11	0.93 ± 0.08	1.16 ± 0.08*	1.36 ± 0.07**
Day 24	1.09 ± 0.16	1.03 ± 0.12	1.19 ± 0.07	0.98 ± 0.12	1.51 ± 0.21	1.67 ± 0.14**
Week 14	1.44 ± 0.16	1.37 ± 0.17	1.32 ± 0.13	1.46 ± 0.16	1.74 ± 0.18	3.00 ± 0.32**
Lymphocytes ($10^3/\mu L$)						
Day 4	6.24 ± 0.34	8.50 ± 0.82	7.56 ± 0.73	7.17 ± 0.85	7.79 ± 0.83	6.33 ± 0.34
Day 24	7.84 ± 0.39	8.06 ± 0.46	8.70 ± 0.45	8.64 ± 0.48	8.10 ± 0.25	8.77 ± 0.38
Week 14	7.99 ± 0.40	6.87 ± 0.31	7.87 ± 0.43	7.56 ± 0.42	7.12 ± 0.39	7.51 ± 0.53

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male (continued)						
Hematology (continued)						
n						
Day 4	9	9	9	9	9	9
Day 24	10	10	10	10	10	10
Week 14	10	10	10	10	10	10
Monocytes ($10^3/\mu L$)						
Day 4	0.11 ± 0.04	0.08 ± 0.03	0.08 ± 0.02	0.16 ± 0.06	0.07 ± 0.02	0.09 ± 0.02
Day 24	0.21 ± 0.04	0.15 ± 0.03	0.13 ± 0.04	0.15 ± 0.05	0.24 ± 0.06	0.14 ± 0.04
Week 14	0.01 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.04 ± 0.02
Eosinophils ($10^3/\mu L$)						
Day 4	0.08 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.10 ± 0.03	0.09 ± 0.04	0.04 ± 0.02
Day 24	0.06 ± 0.03	0.05 ± 0.03	0.07 ± 0.03	0.07 ± 0.03	0.06 ± 0.03	0.04 ± 0.02
Week 14	0.05 ± 0.02	0.04 ± 0.02	0.09 ± 0.02	0.08 ± 0.03	0.04 ± 0.02	0.04 ± 0.03
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	25.8 ± 0.5	26.0 ± 0.5	26.0 ± 0.5	26.1 ± 0.7	25.7 ± 0.7	26.3 ± 0.6
Day 24	23.7 ± 0.6[b]	23.6 ± 0.6	23.8 ± 0.5	23.1 ± 0.4	22.9 ± 0.8	22.3 ± 0.3
Week 14	23.2 ± 0.6	23.5 ± 0.3	22.7 ± 0.9	22.6 ± 0.8	22.8 ± 0.5	23.8 ± 0.8
Creatinine (mg/dL)						
Day 4	0.76 ± 0.02	0.75 ± 0.02	0.74 ± 0.02	0.74 ± 0.02	0.74 ± 0.02	0.74 ± 0.02
Day 24	0.72 ± 0.02[b]	0.72 ± 0.01	0.73 ± 0.02	0.74 ± 0.02	0.71 ± 0.01	0.71 ± 0.02
Week 14	0.70 ± 0.02	0.66 ± 0.02	0.71 ± 0.02	0.69 ± 0.02	0.69 ± 0.02	0.70 ± 0.04
Total protein (g/dL)						
Day 4	6.8 ± 0.1	6.9 ± 0.1	6.9 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	6.8 ± 0.2
Day 24	7.7 ± 0.1	7.6 ± 0.1	7.5 ± 0.1	7.6 ± 0.1	7.6 ± 0.1	7.3 ± 0.1*
Week 14	7.3 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.1 ± 0.1	7.3 ± 0.2
Albumin (g/dL)						
Day 4	4.8 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.8 ± 0.1
Day 24	5.2 ± 0.1[b]	5.2 ± 0.0	5.1 ± 0.0	5.3 ± 0.1	5.2 ± 0.1	5.1 ± 0.1
Week 14	4.9 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	4.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 4	42 ± 1	45 ± 1	44 ± 2	47 ± 3	50 ± 3*	52 ± 4*
Day 24	54 ± 2	57 ± 1	57 ± 2	59 ± 2	62 ± 2	61 ± 4
Week 14	63 ± 3	68 ± 8	71 ± 10	57 ± 2	62 ± 3	87 ± 17
Alkaline phosphatase (IU/L)						
Day 4	1,596 ± 36	1,661 ± 34	1,623 ± 26	1,590 ± 48	1,608 ± 47	1,460 ± 47
Day 24	1,091 ± 26	1,080 ± 15	1,057 ± 24	1,079 ± 34	1,121 ± 20	1,150 ± 26
Week 14	516 ± 20	541 ± 12	543 ± 17	541 ± 19	557 ± 29	656 ± 26**
Sorbitol dehydrogenase (IU/L)						
Day 4	26 ± 1	24 ± 2	23 ± 2	23 ± 2	27 ± 2	26 ± 2
Day 24	24 ± 2	24 ± 1	25 ± 2	23 ± 1	24 ± 1	22 ± 1
Week 14	26 ± 3	23 ± 2[b]	25 ± 3[b]	20 ± 1	23 ± 2	33 ± 8
Bile salts (μmol/L)						
Day 4	43.8 ± 6.4	27.9 ± 3.7	41.8 ± 9.4	29.6 ± 4.3	31.2 ± 4.3	25.3 ± 4.4*
Day 24	49.1 ± 6.5	39.9 ± 6.7	35.2 ± 6.2	30.5 ± 3.9	35.9 ± 7.5	49.9 ± 9.6
Week 14	26.7 ± 4.6	19.4 ± 1.6	23.2 ± 2.1	20.8 ± 1.9	23.2 ± 3.8	26.2 ± 4.4

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Female						
Hematology						
n						
Day 4	10	10	10	10	10	10
Day 24	10	10	10	10	10	10
Week 14	10	10	10	9	10	10
Hematocrit (%)						
Day 4	49.1 ± 0.4	47.7 ± 0.5	48.2 ± 0.5	48.7 ± 0.9	47.9 ± 0.6	47.5 ± 0.6
Day 24	51.7 ± 0.3	51.2 ± 0.3	52.1 ± 0.6	52.9 ± 1.3	51.3 ± 0.7	51.3 ± 0.6
Week 14	46.7 ± 0.4	46.2 ± 0.7	46.9 ± 0.9	47.1 ± 0.8	45.5 ± 0.4	45.1 ± 0.6
Hemoglobin (g/dL)						
Day 4	16.4 ± 0.1	15.8 ± 0.2	16.0 ± 0.1	16.3 ± 0.3	16.0 ± 0.2	15.9 ± 0.2
Day 24	17.4 ± 0.1	17.4 ± 0.1	17.5 ± 0.2	17.8 ± 0.3	17.3 ± 0.1	17.3 ± 0.1
Week 14	15.7 ± 0.2	15.8 ± 0.2	15.9 ± 0.2	16.0 ± 0.2	15.5 ± 0.1	15.5 ± 0.2
Erythrocytes ($10^6/\mu L$)						
Day 4	7.94 ± 0.08	7.66 ± 0.07	7.80 ± 0.09	7.88 ± 0.13	7.69 ± 0.11	7.66 ± 0.12
Day 24	8.24 ± 0.05	8.20 ± 0.05	8.28 ± 0.09	8.45 ± 0.20	8.19 ± 0.11	8.23 ± 0.10
Week 14	7.78 ± 0.08	7.74 ± 0.11	7.81 ± 0.15	7.92 ± 0.12	7.61 ± 0.07	7.57 ± 0.11
Reticulocytes ($10^6/\mu L$)						
Day 4	0.28 ± 0.02	0.24 ± 0.01	0.23 ± 0.01	0.25 ± 0.02	0.25 ± 0.02	0.29 ± 0.02
Day 24	0.17 ± 0.02	0.17 ± 0.01	0.16 ± 0.01	0.16 ± 0.02	0.16 ± 0.01	0.19 ± 0.01
Week 14	0.19 ± 0.02	0.18 ± 0.01	0.16 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.22 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.05 ± 0.03	0.03 ± 0.02	0.10 ± 0.03	0.09 ± 0.05	0.02 ± 0.01	0.02 ± 0.01
Day 24	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01[b]	0.03 ± 0.02	0.03 ± 0.02
Week 14	0.07 ± 0.03	0.05 ± 0.02	0.05 ± 0.02	0.08 ± 0.02	0.07 ± 0.03	0.04 ± 0.02
Mean cell volume (fL)						
Day 4	61.8 ± 0.2	62.2 ± 0.1	61.7 ± 0.2	61.8 ± 0.2	62.3 ± 0.4	62.1 ± 0.3
Day 24	62.8 ± 0.2	62.5 ± 0.1	62.9 ± 0.3	62.6 ± 0.2	62.6 ± 0.2	62.3 ± 0.2
Week 14	60.0 ± 0.1	59.7 ± 0.3	60.0 ± 0.2	59.4 ± 0.3	59.8 ± 0.1	59.5 ± 0.2
Mean cell hemoglobin (pg)						
Day 4	20.6 ± 0.1	20.6 ± 0.1	20.5 ± 0.1	20.6 ± 0.1	20.8 ± 0.1	20.7 ± 0.1
Day 24	21.1 ± 0.2	21.2 ± 0.2	21.1 ± 0.1	21.1 ± 0.2	21.1 ± 0.1	21.1 ± 0.1
Week 14	20.2 ± 0.1	20.5 ± 0.1	20.4 ± 0.1	20.2 ± 0.1	20.4 ± 0.2	20.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 4	33.4 ± 0.2	33.1 ± 0.1	33.3 ± 0.2	33.4 ± 0.1	33.3 ± 0.2	33.4 ± 0.1
Day 24	33.6 ± 0.3	33.9 ± 0.2	33.6 ± 0.3	33.8 ± 0.3	33.8 ± 0.2	33.8 ± 0.2
Week 14	33.6 ± 0.2	34.3 ± 0.3*	34.0 ± 0.3	34.0 ± 0.2	34.1 ± 0.3	34.4 ± 0.2
Platelets ($10^3/\mu L$)						
Day 4	854.8 ± 17.6	843.5 ± 17.2	831.3 ± 21.6	862.3 ± 13.6	828.7 ± 18.2	856.9 ± 19.8
Day 24	771.9 ± 12.0	752.2 ± 10.4	774.7 ± 18.2	790.8 ± 19.4	735.4 ± 11.7	761.3 ± 13.3
Week 14	674.9 ± 15.0	694.3 ± 14.2	704.2 ± 19.7	659.1 ± 27.9	708.1 ± 16.7	696.6 ± 16.1
Leukocytes ($10^3/\mu L$)						
Day 4	11.22 ± 0.44	11.07 ± 0.36	10.54 ± 0.35	11.89 ± 0.49	11.37 ± 0.35	12.27 ± 0.59
Day 24	10.50 ± 0.59	10.01 ± 0.37	9.45 ± 0.51	10.70 ± 0.34[b]	9.66 ± 0.32	10.93 ± 0.54
Week 14	7.30 ± 0.40	6.89 ± 0.31	7.59 ± 0.42	6.84 ± 0.27	7.63 ± 0.34	9.12 ± 0.73
Segmented neutrophils ($10^3/\mu L$)						
Day 4	0.98 ± 0.10	0.95 ± 0.09	1.03 ± 0.15	1.13 ± 0.16	1.24 ± 0.14	1.74 ± 0.26
Day 24	1.42 ± 0.16	1.20 ± 0.14	1.19 ± 0.13	1.47 ± 0.11[b]	1.40 ± 0.17	1.88 ± 0.23
Week 14	1.07 ± 0.10	1.17 ± 0.13	1.56 ± 0.24	1.34 ± 0.22	1.51 ± 0.21	2.57 ± 0.24**
Lymphocytes ($10^3/\mu L$)						
Day 4	10.03 ± 0.38	10.02 ± 0.39	9.28 ± 0.25	10.56 ± 0.50	10.02 ± 0.32	10.30 ± 0.45
Day 24	8.88 ± 0.57	8.69 ± 0.32	8.12 ± 0.51	9.06 ± 0.40[b]	8.20 ± 0.30	8.82 ± 0.49
Week 14	5.90 ± 0.36	5.50 ± 0.28	5.83 ± 0.34	5.26 ± 0.24	5.80 ± 0.15	6.18 ± 0.67

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Female (continued)						
Hematology (continued)						
n						
Day 4	10	10	10	10	10	10
Day 24	10	10	10	10	10	10
Week 14	10	10	10	9	10	10
Monocytes ($10^3/\mu L$)						
Day 4	0.07 ± 0.03	0.05 ± 0.02	0.11 ± 0.03	0.05 ± 0.02	0.04 ± 0.02	0.08 ± 0.01
Day 24	0.11 ± 0.05	0.07 ± 0.02	0.06 ± 0.02	0.09 ± 0.01[b]	0.05 ± 0.02	0.12 ± 0.03
Week 14	0.22 ± 0.03	0.14 ± 0.03	0.14 ± 0.03	0.20 ± 0.04	0.21 ± 0.04	0.18 ± 0.04
Eosinophils ($10^3/\mu L$)						
Day 4	0.13 ± 0.03	0.05 ± 0.02	0.11 ± 0.02	0.12 ± 0.05	0.06 ± 0.02	0.10 ± 0.02
Day 24	0.09 ± 0.02	0.06 ± 0.02	0.08 ± 0.03	0.08 ± 0.03[b]	0.01 ± 0.01*	0.10 ± 0.04
Week 14	0.12 ± 0.03	0.10 ± 0.03	0.06 ± 0.02	0.10 ± 0.03	0.12 ± 0.03	0.18 ± 0.04
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	24.1 ± 0.8	22.0 ± 0.6	23.0 ± 0.9	22.6 ± 0.8	24.0 ± 0.7	23.1 ± 0.6
Day 24	25.9 ± 0.6	25.8 ± 0.6	25.8 ± 1.0	25.0 ± 0.7	25.5 ± 0.3	24.1 ± 0.7
Week 14	23.3 ± 0.5	23.2 ± 0.8	23.2 ± 0.7	24.0 ± 0.7	22.3 ± 0.6	23.1 ± 0.8
Creatinine (mg/dL)						
Day 4	0.68 ± 0.02	0.64 ± 0.02	0.68 ± 0.03	0.68 ± 0.03	0.67 ± 0.02	0.64 ± 0.02
Day 24	0.74 ± 0.02	0.76 ± 0.02	0.76 ± 0.03	0.76 ± 0.02	0.74 ± 0.02	0.73 ± 0.02
Week 14	0.68 ± 0.04	0.67 ± 0.02	0.68 ± 0.01	0.69 ± 0.03	0.69 ± 0.02	0.65 ± 0.02
Total protein (g/dL)						
Day 4	6.6 ± 0.1	6.4 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	6.3 ± 0.1	6.4 ± 0.1
Day 24	7.1 ± 0.1	7.2 ± 0.1	7.1 ± 0.1	7.3 ± 0.1	7.2 ± 0.1	7.1 ± 0.1
Week 14	6.8 ± 0.1	7.0 ± 0.2	7.0 ± 0.1	6.9 ± 0.1	6.8 ± 0.1	6.8 ± 0.1
Albumin (g/dL)						
Day 4	4.7 ± 0.1	4.5 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.6 ± 0.1
Day 24	5.0 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.2 ± 0.0	5.2 ± 0.0	5.2 ± 0.1
Week 14	4.7 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 4	43 ± 1	40 ± 1	42 ± 1	45 ± 2	45 ± 1	46 ± 2
Day 24	42 ± 1	42 ± 1	49 ± 6	43 ± 2	42 ± 1	45 ± 1
Week 14	54 ± 4	58 ± 4	65 ± 7	75 ± 7*	48 ± 3	54 ± 3
Alkaline phosphatase (IU/L)						
Day 4	1,302 ± 35	1,234 ± 24	1,279 ± 29	1,270 ± 40	1,250 ± 52	1,247 ± 53
Day 24	977 ± 23	990 ± 26	1,002 ± 33	985 ± 26	1,030 ± 25	1,035 ± 30
Week 14	537 ± 20	580 ± 22	549 ± 19	583 ± 30	607 ± 15	585 ± 8

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Sorbitol dehydrogenase (IU/L)						
Day 4	22 ± 2	19 ± 1	21 ± 2	19 ± 2	22 ± 1	19 ± 1
Day 24	28 ± 1	27 ± 2	28 ± 1[b]	26 ± 2	23 ± 1	27 ± 2
Week 14	20 ± 2	21 ± 2	21 ± 3	32 ± 6	18 ± 2	18 ± 2
Bile salts (μmol/L)						
Day 4	34.5 ± 5.2	31.9 ± 3.4	38.7 ± 4.4	25.7 ± 3.3	32.0 ± 6.1	33.0 ± 6.0
Day 24	38.3 ± 4.7	42.4 ± 5.5	35.6 ± 5.8	33.2 ± 5.7	26.3 ± 4.1	19.9 ± 1.6**
Week 14	37.7 ± 3.7	54.3 ± 11.8	34.3 ± 3.2	34.3 ± 6.4	24.9 ± 3.8*	19.4 ± 1.8**

* Significantly different ($P \leq 0.05$) from the vehicle 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 14-Week Dermal Study of Lauric 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	372 ± 6	371 ± 4	370 ± 5	366 ± 5	340 ± 4**	323 ± 4**
Heart						
Absolute	1.128 ± 0.025	1.144 ± 0.030	1.123 ± 0.013	1.141 ± 0.031	1.093 ± 0.028	1.105 ± 0.019
Relative	3.03 ± 0.05	3.08 ± 0.07	3.04 ± 0.06	3.12 ± 0.06	3.21 ± 0.06*	3.42 ± 0.05**
R. Kidney						
Absolute	1.389 ± 0.030	1.416 ± 0.017	1.419 ± 0.018	1.438 ± 0.032	1.387 ± 0.022	1.395 ± 0.020
Relative	3.73 ± 0.05	3.82 ± 0.04	3.84 ± 0.03	3.93 ± 0.05**	4.08 ± 0.05**	4.33 ± 0.06**
Liver						
Absolute	16.483 ± 0.505	17.093 ± 0.401	17.085 ± 0.392	16.664 ± 0.498	15.303 ± 0.254	14.557 ± 0.324**
Relative	44.22 ± 0.83	46.08 ± 1.03	46.14 ± 0.75	45.53 ± 1.09	45.01 ± 0.53	45.14 ± 0.97
Lung						
Absolute	1.874 ± 0.081	1.932 ± 0.056	1.818 ± 0.059	2.010 ± 0.060[b]	1.670 ± 0.071	1.828 ± 0.106
Relative	5.04 ± 0.21	5.21 ± 0.14	4.92 ± 0.18	5.51 ± 0.13[b]	4.91 ± 0.18	5.66 ± 0.32
R. Testis						
Absolute	1.518 ± 0.028	1.540 ± 0.017	1.526 ± 0.016	1.487 ± 0.036	1.449 ± 0.031	1.466 ± 0.015
Relative	4.08 ± 0.07	4.16 ± 0.07	4.13 ± 0.06	4.06 ± 0.08	4.26 ± 0.09	4.55 ± 0.07**
Thymus						
Absolute	0.383 ± 0.028	0.379 ± 0.033	0.343 ± 0.014	0.337 ± 0.012	0.344 ± 0.025	0.304 ± 0.033
Relative	1.03 ± 0.08	1.02 ± 0.08	0.93 ± 0.03	0.92 ± 0.03	1.01 ± 0.07	0.94 ± 0.10
Female						
Necropsy body wt	195 ± 5	200 ± 4	199 ± 3	189 ± 4	193 ± 3	185 ± 4
Heart						
Absolute	0.740 ± 0.020	0.720 ± 0.015	0.712 ± 0.013	0.716 ± 0.012	0.747 ± 0.015	0.750 ± 0.022
Relative	3.81 ± 0.06	3.61 ± 0.08	3.58 ± 0.08	3.80 ± 0.09	3.87 ± 0.07	4.06 ± 0.14
R. Kidney						
Absolute	0.792 ± 0.018	0.817 ± 0.018	0.840 ± 0.013	0.822 ± 0.008	0.891 ± 0.016**	0.916 ± 0.017**
Relative	4.07 ± 0.04	4.09 ± 0.05	4.22 ± 0.05	4.36 ± 0.09**	4.62 ± 0.06**	4.94 ± 0.06**
Liver						
Absolute	7.543 ± 0.267	7.895 ± 0.255	7.940 ± 0.157	7.627 ± 0.141	7.917 ± 0.162	8.077 ± 0.211
Relative	38.66 ± 0.53	39.50 ± 0.78	39.86 ± 0.74	40.45 ± 0.92	41.00 ± 0.66*	43.59 ± 0.93**
Lung						
Absolute	1.330 ± 0.035	1.309 ± 0.027	1.423 ± 0.064[b]	1.263 ± 0.061	1.216 ± 0.038	1.313 ± 0.065
Relative	6.86 ± 0.20	6.59 ± 0.22	7.18 ± 0.34[b]	6.71 ± 0.38	6.31 ± 0.24	7.12 ± 0.43
Thymus						
Absolute	0.255 ± 0.007	0.290 ± 0.019	0.257 ± 0.012	0.259 ± 0.015	0.280 ± 0.016	0.229 ± 0.009
Relative	1.31 ± 0.04	1.46 ± 0.10	1.30 ± 0.07	1.37 ± 0.08	1.45 ± 0.09	1.23 ± 0.04

* Significantly different (P≤0.05) from the vehicle control group by Williams' or Dunnett's test
** P≤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).
[b] n=9

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
n	10	10	10	10	10	10
Male						
Necropsy body wt	36.4 ± 0.9	34.8 ± 0.3	35.8 ± 0.6	33.4 ± 0.6**	34.7 ± 0.4	34.4 ± 0.4
Heart						
Absolute	0.178 ± 0.005	0.194 ± 0.007	0.203 ± 0.008*	0.184 ± 0.004	0.191 ± 0.003	0.191 ± 0.006
Relative	4.90 ± 0.14	5.56 ± 0.22*	5.70 ± 0.26**	5.52 ± 0.10	5.51 ± 0.08	5.54 ± 0.14*
R. Kidney						
Absolute	0.333 ± 0.012	0.354 ± 0.008	0.365 ± 0.008*	0.357 ± 0.008	0.375 ± 0.008**	0.387 ± 0.012**
Relative	9.14 ± 0.26	10.15 ± 0.19**	10.22 ± 0.30**	10.69 ± 0.21**	10.79 ± 0.16**	11.24 ± 0.30**
Liver						
Absolute	1.824 ± 0.048	1.822 ± 0.035	1.859 ± 0.028	1.720 ± 0.042	1.793 ± 0.031	1.930 ± 0.044
Relative	50.16 ± 1.14	52.29 ± 0.89	52.01 ± 1.15	51.47 ± 1.00	51.63 ± 0.51	56.09 ± 0.94**
Lung						
Absolute	0.248 ± 0.014	0.231 ± 0.004	0.237 ± 0.005	0.229 ± 0.008	0.256 ± 0.014	0.239 ± 0.008
Relative	6.82 ± 0.38	6.64 ± 0.15	6.63 ± 0.17	6.85 ± 0.16	7.39 ± 0.44	6.95 ± 0.23
R. Testis						
Absolute	0.129 ± 0.003	0.121 ± 0.004	0.124 ± 0.002	0.121 ± 0.002	0.124 ± 0.002	0.131 ± 0.003
Relative	3.56 ± 0.09	3.46 ± 0.13	3.46 ± 0.06	3.62 ± 0.09	3.59 ± 0.07	3.80 ± 0.09
Thymus						
Absolute	0.052 ± 0.003	0.052 ± 0.003	0.052 ± 0.003	0.047 ± 0.003	0.040 ± 0.002*	0.045 ± 0.004*
Relative	1.44 ± 0.07	1.48 ± 0.09	1.46 ± 0.09	1.40 ± 0.08	1.16 ± 0.06	1.32 ± 0.11
Female						
Necropsy body wt	31.2 ± 0.8	31.2 ± 0.6	31.6 ± 1.0	30.7 ± 0.8	30.3 ± 0.4	30.1 ± 0.5
Heart						
Absolute	0.164 ± 0.006	0.162 ± 0.006	0.162 ± 0.004	0.164 ± 0.006	0.170 ± 0.005	0.179 ± 0.008
Relative	5.27 ± 0.19	5.20 ± 0.17	5.18 ± 0.19	5.35 ± 0.13	5.59 ± 0.12	5.95 ± 0.20**
R. Kidney						
Absolute	0.251 ± 0.006	0.242 ± 0.005	0.248 ± 0.005	0.254 ± 0.004	0.257 ± 0.005	0.276 ± 0.007**
Relative	8.06 ± 0.16	7.77 ± 0.12	7.89 ± 0.20	8.32 ± 0.14	8.46 ± 0.11	9.19 ± 0.10**
Liver						
Absolute	1.583 ± 0.041	1.590 ± 0.039	1.661 ± 0.026	1.702 ± 0.045*	1.755 ± 0.037**	1.848 ± 0.049**
Relative	50.87 ± 1.11	50.98 ± 0.87	52.89 ± 1.09	55.48 ± 0.42**	57.83 ± 0.86**	61.42 ± 0.84**
Lung						
Absolute	0.230 ± 0.007	0.237 ± 0.006	0.248 ± 0.009	0.247 ± 0.012	0.237 ± 0.006	0.263 ± 0.021
Relative	7.40 ± 0.20	7.61 ± 0.19	7.90 ± 0.25	8.10 ± 0.45	7.83 ± 0.23	8.73 ± 0.61*
Thymus						
Absolute	0.059 ± 0.003	0.065 ± 0.003	0.057 ± 0.003	0.056 ± 0.002	0.054 ± 0.002	0.058 ± 0.002
Relative	1.90 ± 0.08	2.07 ± 0.08	1.80 ± 0.07	1.82 ± 0.07	1.77 ± 0.07	1.94 ± 0.07

* Significantly different ($P \leq 0.05$) from the vehicle 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

TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Dermal Study of Lauric 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	372 ± 6	366 ± 5	340 ± 4**	323 ± 4**
L. cauda epididymis	0.1586 ± 0.0027	0.1499 ± 0.0061	0.1566 ± 0.0034	0.1483 ± 0.0036
L. epididymis	0.4541 ± 0.0042	0.4650 ± 0.0093	0.4633 ± 0.0086	0.4367 ± 0.0054
L. testis	1.5868 ± 0.0265	1.5720 ± 0.0400	1.5673 ± 0.0285	1.4988 ± 0.0180
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.56 ± 0.25	9.67 ± 0.28	8.89 ± 0.25	9.84 ± 0.42
Spermatid heads (10^7/testis)	15.20 ± 0.55	15.19 ± 0.53	13.89 ± 0.28	14.77 ± 0.70
Spermatid count (mean/10^{-4} mL suspension)	75.98 ± 2.76	75.93 ± 2.67	69.45 ± 1.42	73.83 ± 3.52
Epididymal spermatozoal measurements				
Motility (%)	72.69 ± 1.99	64.02 ± 3.90	67.27 ± 1.34	59.78 ± 4.81
Concentration (10^6/g cauda epididymal tissue)	756 ± 60	704 ± 68	582 ± 85	586 ± 93

** 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 H2
Estrous Cycle Characterization for Female Rats in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10
Necropsy body wt (g)	195 ± 5	189 ± 4	193 ± 3	185 ± 4
Estrous cycle length (days)	4.90 ± 0.10	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
Estrous stages (% of cycle)				
Diestrus	40.0	38.3	41.7	37.5
Proestrus	16.7	15.0	14.2	19.2
Estrus	23.3	26.7	23.3	22.5
Metestrus	20.0	20.0	20.8	20.8

[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 weights) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females did 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 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
n	10	10	10	10
Weights (g)				
Necropsy body wt	36.4 ± 0.9	33.4 ± 0.6**	34.7 ± 0.4	34.4 ± 0.4
L. cauda epididymis	0.0132 ± 0.0006	0.0147 ± 0.0007	0.0149 ± 0.0006	0.0152 ± 0.0006
L. epididymis	0.0427 ± 0.0009	0.0401 ± 0.0021	0.0425 ± 0.0016	0.0376 ± 0.0025
L. testis	0.1213 ± 0.0018	0.1156 ± 0.0015	0.1189 ± 0.0017	0.1229 ± 0.0022
Spermatid measurements				
Spermatid heads (10^7/g testis)	20.17 ± 0.71	21.06 ± 0.53	20.90 ± 0.64	19.53 ± 0.26
Spermatid heads (10^7/testis)	2.45 ± 0.09	2.43 ± 0.06	2.48 ± 0.07	2.40 ± 0.04
Spermatid count (mean/10^{-4} mL suspension)	76.43 ± 2.83	75.98 ± 1.94	77.58 ± 2.34	74.95 ± 1.36
Epididymal spermatozoal measurements				
Motility (%)	69.04 ± 4.11	68.68 ± 1.63	68.51 ± 2.79	63.62 ± 3.45
Concentration (10^6/g cauda epididymal tissue)	1,683 ± 119	1,786 ± 91	1,390 ± 151	1,523 ± 123

** Significantly different ($P \leq 0.01$) from the vehicle control group by Dunnett's 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
Estrous Cycle Characterization for Female Mice in the 14-Week Dermal Study of Lauric Acid Diethanolamine Condensate[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
n	10	10	10	10
Necropsy body wt (g)	31.2 ± 0.8	30.7 ± 0.8	30.3 ± 0.4	30.1 ± 0.5
Estrous cycle length (days)	4.10 ± 0.10	4.00 ± 0.00	4.30 ± 0.13	4.06 ± 0.06[b]
Estrous stages (% of cycle)				
Diestrus	26.7	30.8	29.2	30.0
Proestrus	22.5	22.5	18.3	19.2
Estrus	26.7	25.0	29.2	28.3
Metestrus	24.2	21.7	23.3	22.5

[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 weights) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females did not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Lauric Acid Diethanolamine Condensate

Lauric acid diethanolamine condensate was obtained from Rhone Poulenc, Inc. (Louisville, KY), in one lot (CH1E952), which was used during the 14-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 lauric acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

Before testing, lauric acid diethanolamine condensate was heated in the original metal drum to approximately 60° C with barrel warmers until the solid liquefied, and then the liquid was stirred approximately 30 minutes with a mechanical stirrer to homogenize it. The chemical was identified as lauric acid diethanolamine condensate by infrared and nuclear magnetic resonance (NMR) spectroscopy. The spectra were consistent with those expected for the structure of lauric acid diethanolamine condensate and with those of a previously analyzed lot (DS42578CG) not used in the current studies (MRI, 1978). The NMR spectrum also indicated the presence of small quantities of unidentified impurities. The infrared and nuclear magnetic spectra are presented in Figures I1 and I2.

The purity of lot CH1E952 was determined by high-performance liquid chromatography (HPLC) and nitrosamine quantitation. HPLC was performed with a Phenomenex Ultracarb 5 ODS (30) column using ultraviolet detection (230 nm) and a solvent system of methanol:water (85:15). The flow rate was 0.5 mL/minute. Thermede Tec, Inc. (Woburn, MA), analyzed polar and nonpolar nitrosamines by HPLC with a thermo-energy analyzer.

HPLC indicated one major peak and four smaller impurity peaks with areas of 0.5% or greater relative to the major peak area. One impurity peak appeared to have multiple components. The HPLC data indicated approximately 5% organic impurities. Based on calculations using the amine value provided by the manufacturer, the unreacted diethanolamine content was estimated at 9.17%. One polar nitrosamine, nitrosodiethanolamine, was detected at a concentration of 3,600 ppb. No nonpolar nitrosamines were detected (detection limits: 10 ppb for volatile nitrosamines; 80 ppb for nonvolatile nitrosamines).

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory on lot DS42578CG by gas chromatography with a flame ionization detector, a 3% SP2100 on 100/120 Supelcoport glass column, an oven temperature of 220° C (isothermal), and a nitrogen carrier gas at a flow rate of 70 mL/minute. Lauric acid diethanolamine condensate showed some instability when stored in glass vials for 2 weeks at 60° C but very little loss below 25° C. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in amber glass bottles sealed with Teflon®-lined caps. Stability was monitored during the 14-week and 2-year studies using HPLC as described for the purity analysis. No degradation of the bulk chemical was detected.

Ethanol

Ethanol (95%) was obtained from Aaper Alcohol and Chemical Company (Shelbyville, KY) in 11 lots. Lot 91D22U was used in the 14-week studies and at the beginning of the 2-year studies; the remaining lots were used throughout the 2-year studies. The purity of the 95% ethanol used in the 14-week and 2-year studies was monitored using gas chromatography with a flame ionization detector at the beginning and

2 weeks after the end of the 14-week studies and every 2 to 4 months during the 2-year studies. The column system used 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 increased to 220° C at a rate of 10° C/minute. USP/NF ethanol reference standards were examined concomitantly. Purity of the bulk ethanol ranged from 97% to 103% relative to the reference standard, 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%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 3 weeks by liquefying and stirring lauric acid diethanolamine condensate at approximately 70° C. A weighed amount of lauric acid diethanolamine condensate was mixed with approximately half the required 95% ethanol, and the mixture sonicated until it appeared to be in solution. The solution was allowed to cool and then diluted to volume with 95% ethanol to give the proper concentration (Table I1). The dose formulations were stored in sealed containers at room temperature, protected from light, for up to 28 days.

Stability studies of the 10 mg/mL dose formulation were performed by the study laboratory using HPLC as described for the bulk purity analyses. Samples stored for 28 days showed slightly lower concentrations of lauric acid diethanolamine condensate; this result was apparently due to an error in the preparation of these samples and not to degradation of the chemical. When stored in sealed glass containers and protected from light, the dose formulations were stable for at least 28 days between -20° C and room temperature. When exposed to air and light, the stability of lauric acid diethanolamine condensate was confirmed for three hours; however, there was a 1% loss of weight and it was recommended that precautions be taken to reduce evaporation of the ethanol.

Periodic analyses of the dose formulations of lauric acid diethanolamine condensate were conducted at the study laboratory using HPLC. For the 14-week studies, dose formulations from the beginning, middle, and end of the studies were analyzed (Table I2). During the 2-year studies, dose formulations were analyzed approximately every 2 months (Table I3). During the 14-week studies, 60% (9/15) of the dose formulations for rats and 67% (10/15) for mice were within 10% of the target concentration; one rat dose formulation from the initial analysis and all rat and mouse dose formulations from the second analysis were more than 10% less than the target concentrations. The one rat dose formulation from the initial analysis was remixed. The dose formulations from the second analysis were remixed using a freshly opened bottle of lauric acid diethanolamine condensate; all remixes were within 10% of the target concentrations. Throughout the 2-year studies, a fresh bottle of lauric acid diethanolamine condensate was used for each set of dose formulations. All 48 dose formulations analyzed during the 2-year studies were within 10% of the target concentration, with no value greater than 108%. In addition to dose formulation analysis prior to dosing, samples collected after dosing (animal room samples) were analyzed periodically. All 30 animal room samples from formulations analyzed during the 14-week studies were within 10% of the target concentration. For the 2-year studies, 94% (15/16) were within 10% of the target concentration. One sample was 126% of the target concentration; this was attributed to evaporation of the 95% ethanol vehicle.

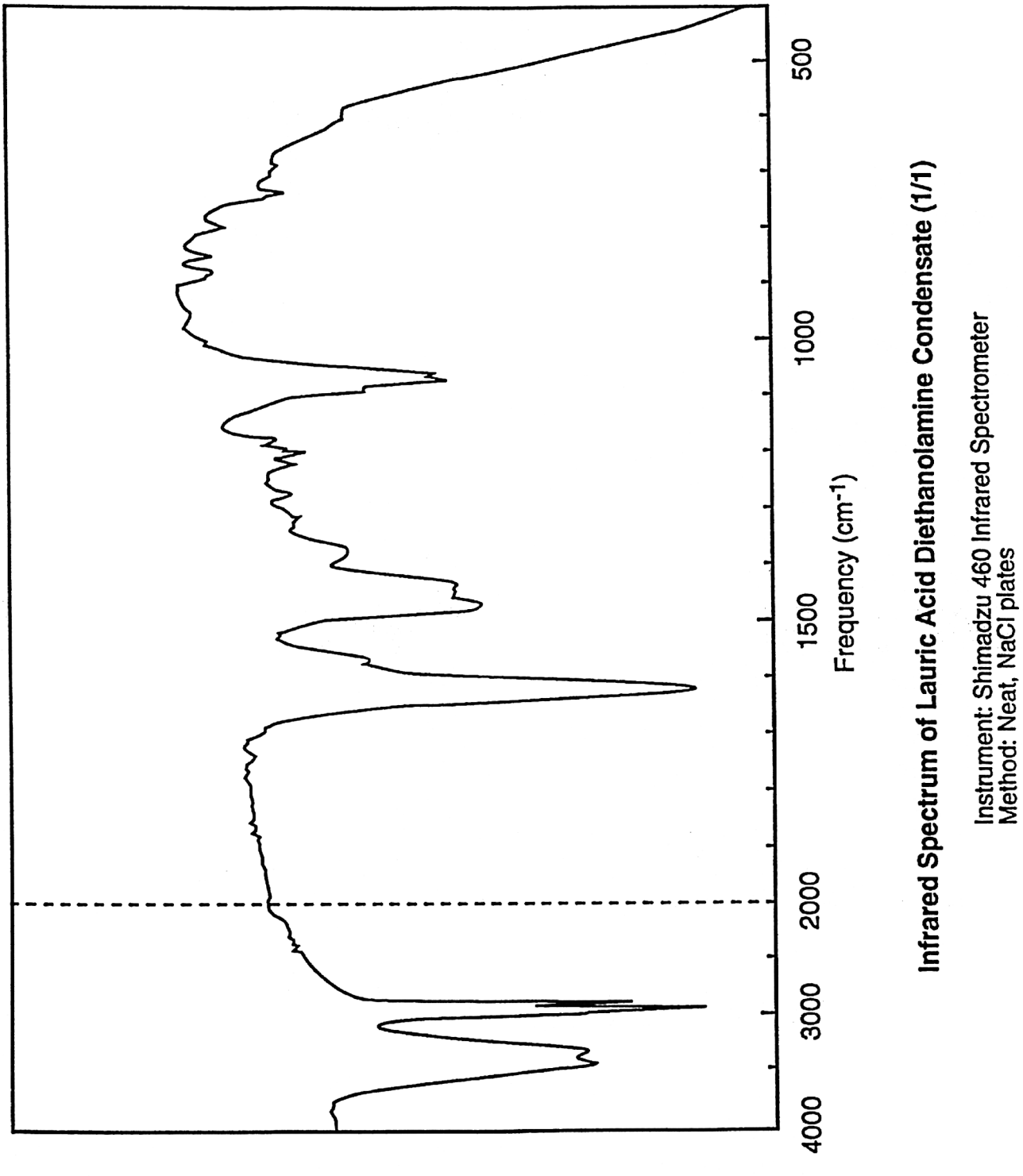

FIGURE I1
Infrared Absorption Spectrum of Lauric Acid Diethanolamine Condensate

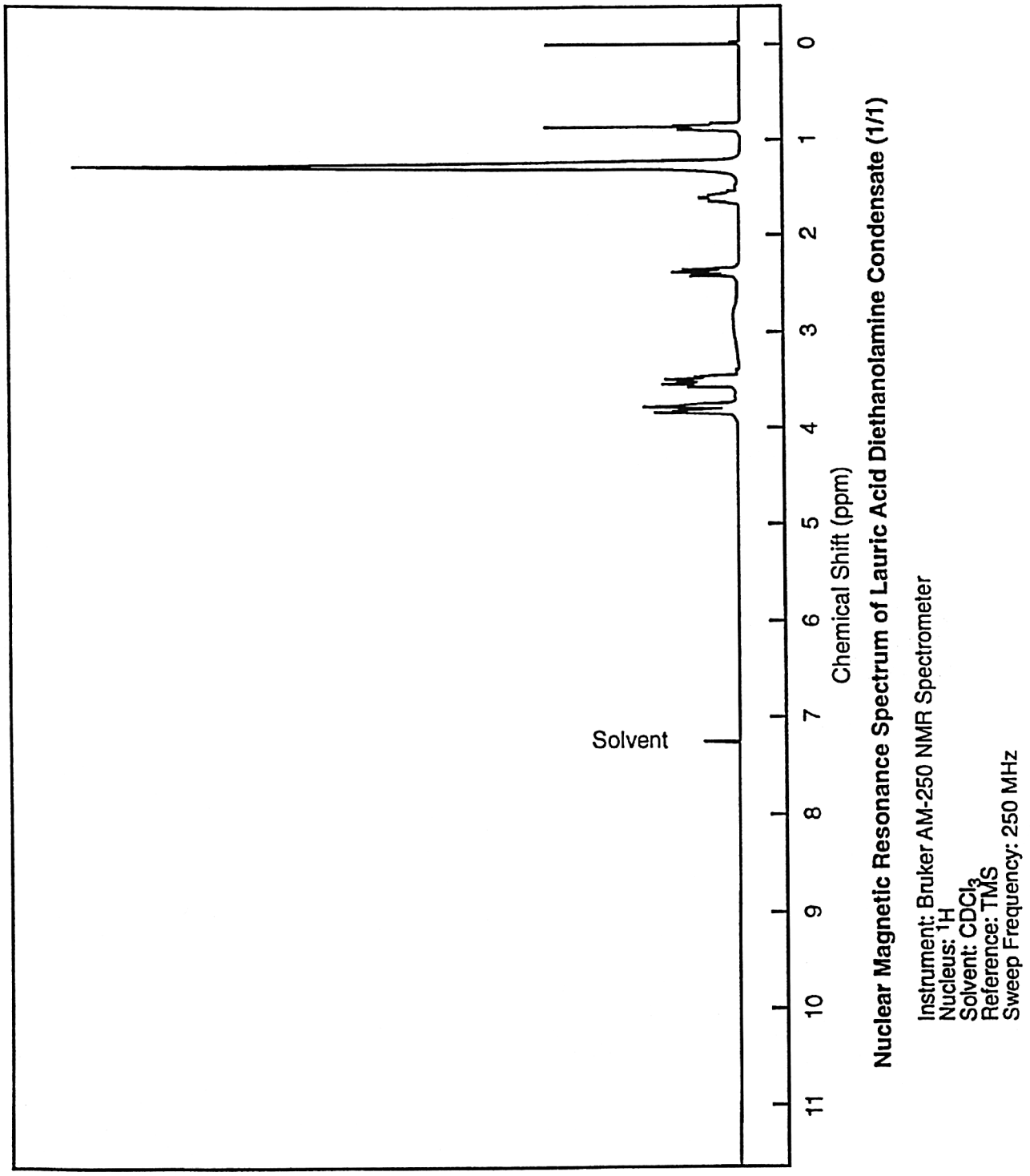

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Lauric Acid Diethanolamine Condensate

TABLE I1
Preparation and Storage of Dose Formulations in the Dermal Studies of Lauric Acid Diethanolamine Condensate

14-Week Studies	2-Year Studies
Preparation The dose formulations were prepared every 3 weeks by liquefying lauric acid diethanolamine condensate at approximately 70° C, stirring during the heating process. The proper amount of lauric acid diethanolamine condensate for each dose concentration was added to approximately half the required 95% ethanol, and the mixture was sonicated until it appeared to be in solution. The solution was allowed to cool and then diluted to volume with 95% ethanol to give the proper concentration.	Same as 14-week studies
Chemical Lot Number CH1E952	Same as 14-week studies
Maximum Storage Time 28 days	Same as 14-week studies
Storage Conditions Stored in sealed containers, protected from light, at room temperature	Same as 14-week studies
Study Laboratory Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Dermal Studies of Lauric Acid Diethanolamine Condensate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
6 January 1992	7 January 1992	30	28.9	−4
		61	53.9	−12
		121	117	−3
		243	235	−3
		485	466	−4
10 January 1992	10 January 1992	61	57.7[b]	−5
	3 February 1992[c]	30	28.3	−6
		61	56.9	−7
		121	111	−8
		243	223	−8
		485	445	−8
17 February 1992	18 February 1992	30	25.0	−17
		61	52.2	−14
		121	103	−15
		243	211	−13
		485	415	−14
22 February 1992	22 February 1992	30	30.5[b]	+2
		61	61.6[b]	+1
		121	121[b]	0
		243	237[b]	−2
		485	482[b]	−1
	13 March 1992[c]	30	29.4	−2
		61	60.1	−1
		121	121	0
		243	243	0
		485	470	−3
30 March 1992	30 March 1992	30	27.6	−8
		61	55.7	−9
		121	112	−7
		243	223	−8
		485	443	−9
	23-24 April 1992[c]	30	27.6	−8
		61	55.6	−9
		121	112	−7
		243	225	−7
		485	443	−9

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Dermal Studies of Lauric Acid Diethanolamine Condensate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice				
6 January 1992	7 January 1992	20	19.4	−3
		40	38.5	−4
		80	75.6	−5
		160	153	−4
		320	314	−2
	3 February 1992[c]	20	19.0	−5
		40	37.8	−5
		80	72.7	−9
		160	146	−9
		320	295	−8
17 February 1992	18 February 1992	20	16.7	−16
		40	34.6	−13
		80	67.6	−15
		160	138	−14
		320	278	−13
22 February 1992	22 February 1992	20	20.3[b]	+2
		40	40.4[b]	+1
		80	81.2[b]	+2
		160	155[b]	−3
		320	316[b]	−1
	13 March 1992[c]	20	19.8	−1
		40	39.5	−1
		80	79.0	−1
		160	158	−1
		320	321	0
30 March 1992	30 March 1992	20	18.4	−8
		40	36.9	−8
		80	72.9	−9
		160	147	−8
		320	290	−9
	23-24 April 1992[c]	20	18.7	−6
		40	36.7	−8
		80	74.6	−7
		160	150	−6
		320	292	−9

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 138 to 302 μL (males) and 103 to 159 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 63 to 88 μL (males) and 51 to 79 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; and 320 mg/mL=800 mg/kg.
[b] Results of remix
[c] Animal room samples

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

Date Prepared	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats			
4 December 1992	85	81.5	−4
	170	166	−2
4 December 1992[b]	85	89.6	+5
	170	214	+26
5 February 1993	85	81.8	−4
	170	166	−2
9 April 1993	85	79.5	−6
	170	163	−4
11 June 1993	85	81.0	−5
	170	161	−5
11 June 1993[b]	85	79.1	−7
	170	165	−3
13 August 1993	85	79.1	−7
	170	155	−9
18 October 1993	85	86.2	+1
	170	172	+1
20 December 1993	85	90.2	+6
	170	180	+6
20 December 1993[b]	85	79.4	−7
	170	159	−6
21 February 1994	85	87.0	+2
	170	171	+1
25 April 1994	85	91.7	+8
	170	171	+1
27 June 1994	85	85.8	+1
	170	172	+1
27 June 1994[b]	85	89.9	+6
	170	176	+4
29 August 1994	85	89.8	+6
	170	180	+6
31 October 1994	85	88.3	+4
	170	177	+4

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

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice			
4 December 1992	50	47.5	−5
	100	95.6	−4
4 December 1992[b]	50	51.6	+3
	100	104	+4
5 February 1993	50	47.2	−6
	100	92.9	−7
9 April 1993	50	48.6	−3
	100	95.3	−5
11 June 1993	50	47.0	−6
	100	94.4	−6
11 June 1993[b]	50	46.5	−7
	100	94.4	−6
13 August 1993	50	45.8	−8
	100	92.5	−7
18 October 1993	50	50.0	0
	100	102	+2
20 December 1993	50	52.6	+5
	100	106	+6
20 December 1993[b]	50	47.2	−6
	100	97.4	−3
21 February 1994	50	50.1	0
	100	101	+1
25 April 1994	50	53.7	+7
	100	107	+7
27 June 1994	50	51.9	+4
	100	101	+1
27 June 1994[b]	50	51.9	+4
	100	104	+4
29 August 1994	50	51.3	+3
	100	104	+4
31 October 1994	50	52.3	+5
	100	105	+5

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 72 to 278 μL (males) and 61 to 186 μL (females); 85 mg/mL = 50 mg/kg and 170 mg/mL = 100 mg/kg. For mice, dosing volumes ranged from 46 to 105 μL (males) and 39 to 110 μL (females); 50 mg/mL = 100 mg/kg and 100 mg/mL = 200 mg/kg.
[b] Animal room samples

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[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)	22.97 ± 0.50	22.10 — 23.9	27
Crude fat (% by weight)	5.34 ± 0.15	5.00 — 5.60	27
Crude fiber (% by weight)	3.15 ± 0.29	2.60 — 4.00	27
Ash (% by weight)	6.26 ± 0.18	5.72 — 6.64	27
Amino Acids (% of 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 (% of total diet)			
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)	6,763 ± 486	6,160 — 8,800	27
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)	16.35 ± 2.33	13.0 — 24.0	26
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 (%)	1.15 ± 0.06	1.03 — 1.33	27
Phosphorus (%)	0.89 ± 0.02	0.84 — 0.93	27
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)	0.52 ± 0.15	0.10 — 0.70	27
Cadmium (ppm)	0.04 ± 0.01	0.04 — 0.06	27
Lead (ppm)	0.25 ± 0.07	0.20 — 0.40	27
Mercury (ppm)	<0.02		27
Selenium (ppm)	0.35 ± 0.09	0.10 — 0.50	27
Aflatoxins (ppb)	<5.0		27
Nitrate nitrogen (ppm)[c]	7.70 ± 2.49	3.00 — 14.0	27
Nitrite nitrogen (ppm)[c]	1.12 ± 0.91	0.20 — 3.50	27
BHA (ppm)[d]	2.09 ± 3.98	0.40 — 20.0	27
BHT (ppm)[d]	1.76 ± 1.04	0.40 — 5.0	27
Aerobic plate count (CFU/g)	123,637 ± 132,133	7,200 — 460,000	27
Coliform (MPN/g)	16 ± 41.5	3 — 210	27
Escherichia coli (MPN/g)	5 ± 3.3	3 — 10	27
Salmonella (MPN/g)	Negative		27
Total nitrosoamines (ppb)[e]	11.88 ± 4.02	4.0 — 23.0	27
N-Nitrosodimethylamine (ppb)[e]	9.94 ± 3.96	3.0 — 21.0	27
N-Nitrosopyrrolidine (ppb)[e]	1.94 ± 1.16	1.0 — 6.0	27
Pesticides (ppm)			
α-BHC	<0.01		27
β-BHC[d]	<0.02		27
γ-BHC	<0.01		27
δ-BHC	<0.01		27
Heptachlor	<0.01		27
Aldrin	<0.01		27
Heptachlor epoxide	<0.01		27
DDE	<0.01		27
DDD	<0.01		27
DDT	<0.01		27
HCB	<0.01		27
Mirex	<0.01		27
Methoxychlor	<0.05		27
Dieldrin	<0.01		27
Endrin	<0.01		27
Telodrin	<0.01		27
Chlordane	<0.05		27
Toxaphene	<0.10		27
Estimated PCBs	<0.20		27
Ronnel	<0.01		27
Ethion	<0.02		27
Trithion	<0.05		27
Diazinon	<0.10		27
Methyl parathion	<0.02		27
Ethyl parathion	<0.02		27
Malathion	0.09 ± 0.07	0.02 — 0.30	27
Endosulfan I	<0.01		27
Endosulfan II	<0.01		27
Endosulfan sulfate	<0.03		27

[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

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 14-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	
14-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
Immunofluorescence Assay	
Parvovirus	18 months
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	
14-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	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, study termination
Mouse adenoma virus	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	
EDIM	12 months
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 of serology tests are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 14-Week and 2-Year Dermal Studies of Lauric Acid Diethanolamine Condensate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Studies		
Rats		
Study termination	0/10	
Mice		
Study termination	0/10	
2-Year Studies		
Rats		
1 Month	0/10	
6 Months	0/10	
12 Months	0/10	
18 Months	1/8	H-1
	2/8	Parvovirus
Study termination	4/10[a]	*M. arthritidis*
Mice		
1 Month	0/10	
6 Months	0/10	
12 Months	0/10	
18 Months	0/9	
Study termination	4/10[a]	*M. arthritidis*

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