NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

(CAS NO. 68603-42-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

January 2001

NTP TR 479

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

FOREWORD

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

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

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

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

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP reports printed since 1982 appears on the inside back cover.

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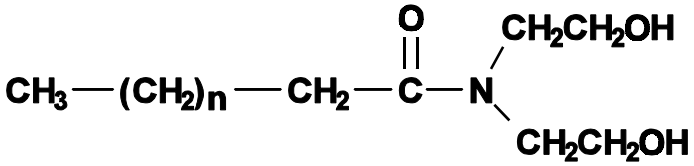
ABSTRACT



n = 7, 9, 11, 13, or 15

COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

CAS No. 68603-42-9

Chemical Formula: $C_{(7+n)}H_{(15+2n)}O_3N$ Molecular Weight: 280-290

Synonyms: Cocamide DEA; cocamide diethanolamine; coconut oil diethanolamine; N,N-bis(hydroxyethyl)coco amides; N,N-bis(hydroxyethyl)coco fatty amides

Trade names: Clindrol 200CGN; Clindrol 202CGN; Clindrol Superamide 100CG; Comperlan KD; Comperlan LS; Comperlan PD; Conco Emulsifier K; Elromid KD 80; Empilan CDE; Ethylan LD; Ethylan A 15; Lauridit KDG; Marlamid D 1218; Monamid 150D; Monamid 150DB; Ninol 1281; Ninol 2012E; Ninol 2012 Extra; Ninol P 621; P and G Amide 72; Purton CFD; Schercomid CDA; Steinamid DC 2129; Steinamid DC 2129E; Varamide A 2; Varamide A 10; Varamide A 83; Witcamide 82; Witcamide 5133

Coconut oil acid diethanolamine condensate, a mixture of fatty acid diethanolamides of the acids found in coconut oil, is widely used in cosmetics, shampoos, soaps, and related consumer products. Because of the lack of information about potential risks associated with long-term exposure, coconut oil acid diethanolamine condensate was selected as a representative of the diethanolamine chemical class for evaluation of toxicity and carcinogenic potential.

Male and female F344/N rats and B6C3F$_1$ mice received dermal applications of coconut oil acid diethanolamine condensate 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 F344/N rats received dermal applications of 0, 25, 50, 100, 200, or 400 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol, five times per week for 14 weeks. All rats survived until the end of the study. Final mean body weights and body weight gains of 200 and 400 mg/kg males and females were significantly less than those of the vehicle controls. Clinical findings included irritation of the skin at the site of application in 100, 200, and 400 mg/kg males and females. Cholesterol concentrations were significantly decreased in 200 and 400 mg/kg males and in females administered 100 mg/kg or greater; triglyceride concentrations were also decreased in 200 and 400 mg/kg males. Histopathologic lesions of the skin at the site of application included epidermal

hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis, and ulcer. The incidences and severities of these skin lesions generally increased with increasing dose in males and females. The incidences of renal tubule regeneration in 100, 200, and 400 mg/kg females were significantly greater than the vehicle control incidence, and the severities in 200 and 400 mg/kg females were increased.

14-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice received dermal applications of 0, 50, 100, 200, 400, or 800 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol, five times per week for 14 weeks. All mice survived until the end of the study. Final mean body weights and body weight gains of dosed males and females were similar to those of the vehicle controls. The only treatment-related clinical finding was irritation of the skin at the site of application in males and females administered 800 mg/kg. Weights of the liver and kidney of 800 mg/kg males and females, the liver of 400 mg/kg females, and the lung of 800 mg/kg females were significantly increased compared to the vehicle controls. Epididymal spermatozoal concentration was significantly increased in 800 mg/kg males. Histopathologic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis, and ulcer. The incidences and severities of these skin lesions generally increased with increasing dose in males and females.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats received dermal applications of 0, 50, or 100 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol five times a week for 104 weeks.

Survival, Body Weights, and Clinical Findings

The survival rates of treated male and female rats were similar to those of the vehicle controls. The mean body weights of dosed males and females were similar to those of the vehicle controls throughout most of the study. The only chemical-related clinical finding was irritation of the skin at the site of application in 100 mg/kg females.

Pathology Findings

There were marginal increases in the incidences of renal tubule adenoma or carcinoma (combined) in 50 mg/kg females. The severity of nephropathy increased with increasing dose in female rats. Nonneoplastic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, parakeratosis, and hyperkeratosis, and the incidences and severities of these lesions increased with increasing dose. The incidences of chronic active inflammation, epithelial hyperplasia, and epithelial ulcer of the forestomach increased with dose in female rats, and the increases were significant in the 100 mg/kg group.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice received dermal applications of 0, 100, or 200 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol five times a week for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed male and female mice was generally similar to that of the vehicle controls. Mean body weights of 100 mg/kg females from week 93 and 200 mg/kg females from week 77 were less than those of the vehicle controls. The only clinical finding attributed to treatment was irritation of the skin at the site of application in males administered 200 mg/kg.

Pathology Findings

The incidences of hepatic neoplasms (hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma) were significantly increased in male and/or female mice. Most of the incidences exceeded the historical control ranges. The incidences of eosinophilic foci in dosed groups of male mice were increased relative to that in the vehicle controls.

The incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) were significantly increased in 200 mg/kg males.

Several nonneoplastic lesions of the skin at the site of application were considered treatment related. Incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis were greater in all dosed groups of males and females than in the vehicle controls. The incidences of ulcer in 200 mg/kg males and inflammation and parakeratosis in 200 mg/kg females were greater than those in the vehicle controls.

The incidences of thyroid gland follicular cell hyperplasia in all dosed groups of males and females were significantly greater than those in the vehicle control groups.

GENETIC TOXICOLOGY

Coconut oil acid diethanolamine condensate did not show genotoxic activity *in vitro*. It was not mutagenic in *Salmonella typhimurium*, nor did it produce an increase in mutant L5178Y mouse lymphoma cell colonies. In addition, no increases in the frequencies of sister chromatid exchanges or chromosomal aberrations were observed in Chinese hamster ovary cells after incubation with coconut oil acid diethanolamine condensate. All these *in vitro* assays were conducted with and without induced S9 activation enzymes. In contrast to the uniformly negative results *in vitro*, positive results were obtained in a peripheral blood micronucleus test in male and female mice from the 14-week dermal study.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of coconut oil acid diethanolamine condensate in male F344/N rats administered 50 or 100 mg/kg. There was *equivocal evidence of carcinogenic activity* in female F344/N rats based on a marginal increase in the incidences of renal tubule neoplasms. There was *clear evidence of carcinogenic activity* in male $B6C3F_1$ mice based on increased incidences of hepatic and renal tubule neoplasms and in female $B6C3F_1$ mice based on increased incidences of hepatic neoplasms. These increases were associated with the concentration of free diethanolamine present as a contaminant in the diethanolamine condensate.

Exposure of rats to coconut oil acid diethanolamine condensate by dermal application in ethanol for 2 years resulted in epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, and parakeratosis in males and females and ulcer in females at the site of application. There were increases in the incidences of chronic inflammation, epithelial hyperplasia, and epithelial ulcer in the forestomach of female rats. The severities of nephropathy in dosed female rats were increased.

Exposure of mice to coconut oil acid diethanolamine condensate by dermal application for 2 years resulted in increased incidences of eosinophilic foci of the liver in males. Increased incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in males and females, ulcer in males, and parakeratosis and inflammation in females at the site of application and of follicular cell hyperplasia in the thyroid gland of males and females were chemical related.

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

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Coconut Oil 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	Vehicle control, 50, or 100 mg/kg	Vehicle control, 50, or 100 mg/kg	Vehicle control, 100, or 200 mg/kg	Vehicle control, 100, or 200 mg/kg
Body weights	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls	Dosed groups less than vehicle controls
Survival rates	8/50, 12/50, 11/50	28/50, 24/50, 22/50	41/50, 37/50, 36/50	35/50, 36/50, 26/50
Nonneoplastic effects	Skin, site of application: epidermal hyperplasia (0/50, 46/50, 50/50); sebaceous gland hyperplasia (0/50, 45/50, 50/50); parakeratosis (0/50, 9/50, 28/50); hyperkeratosis (0/50, 36/50, 48/50);	Skin, site of application: epidermal hyperplasia (3/50, 46/50, 50/50); sebaceous gland hyperplasia (2/50, 46/50, 49/50); parakeratosis (1/50, 11/50, 23/50); hyperkeratosis (3/50, 45/50, 47/50); ulcer (2/50, 0/50, 9/50) Forestomach: chronic active inflammation (1/50, 3/50, 10/50); epithelial hyperplasia (2/50, 5/50, 13/50); epithelial ulcer (1/50, 3/50, 11/50) Kidney: severity of nephropathy (1.6, 2.1, 2.7)	Liver: eosinophilic foci (20/50, 29/50, 31/50) Skin, site of application: epidermal hyperplasia (5/50, 47/50, 50/50); sebaceous gland hyperplasia (0/50, 44/50, 49/50); hyperkeratosis (0/50, 24/50, 23/50); ulcer (1/50, 0/50, 7/50) Thyroid gland: follicular cell hyperplasia (11/50, 20/50, 23/50)	Skin, site of application: epidermal hyperplasia (9/50, 47/50, 50/50); sebaceous gland hyperplasia (0/50, 42/50, 48/50); hyperkeratosis (5/50, 30/50, 40/50); chronic active inflammation (3/50, 2/50, 11/50); parakeratosis (3/50, 4/50, 16/50) Thyroid gland: follicular cell hyperplasia (27/50, 36/50, 33/50)
Neoplastic effects	None	None	Liver: hepatocellular adenoma (22/50, 35/50, 45/50); hepatoblastoma (1/50, 1/50, 10/50); hepatocellular adenoma, carcinoma, or hepatoblastoma (29/50, 39/50, 49/50) Kidney: renal tubule adenoma (1/50, 1/50, 7/50); renal tubule adenoma or carcinoma (1/50, 1/50, 9/50)	Liver: hepatocellular adenoma (32/50, 44/50, 43/50); hepatocellular carcinoma (3/50, 21/50, 32/50); hepatocellular adenoma, carcinoma, or hepatoblastoma (33/50, 46/50, 48/50)
Uncertain findings	None	Kidney: renal tubule adenoma or carcinoma (standard evaluation - 0/50, 2/50, 0/50 ; standard and extended evaluations combined - 0/50, 4/50, 1/50)	None	None

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA97, TA98, TA100, and TA1535		
Mouse lymphoma gene mutations:		Negative with or without S9		
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro:*		Negative with or without S9		
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:		Negative with or without S9		
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Positive in males and females		

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 coconut oil acid diethanolamine condensate on 9 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

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

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

Dr. Irwin discussed a logistic regression model designed to quantitatively evaluate the association between hepatocellular neoplasms in female mice and free diethanolamine concentration. He said that this model tended to strengthen the hypothesis that increased incidences of hepatocellular neoplasms in mice are associated with diethanolamine exposure. This model was also applied to the other two diethanolamine condensates tested.

Dr. I. Russo, the first principal reviewer, agreed with the proposed conclusions. She questioned the use of ethanol as the solvent, because coconut oil acid diethanolamine condensate is water soluble. Dr. Irwin responded that the primary purpose for using ethanol as the solvent was to allow comparison of results from all three of the diethanolamides, the other two of which are not water soluble. Furthermore, when water is used as the solvent in dermal studies, the solutions tend to become beaded and do not spread well.

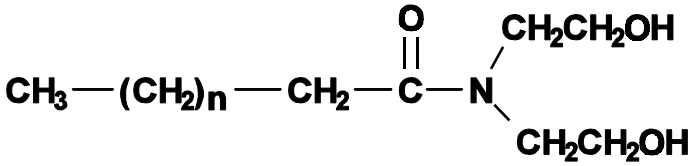
Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions. However, he argued that the statement attributing all the neoplasm responses to free diethanolamine does not appear warranted because the association is mainly supported by data for female mice, while there are gaps of information and a lack of definitive conclusions for the liver as well as for other neoplasm sites. He said that correlations were not assessed for liver neoplasms in male mice. Furthermore, the link between hepatic neoplasm formation and concentrations of free diethanolamine clearly does not apply to hepatoblastoma occurrence. Dr. Irwin agreed that there may be other neoplastic responses not associated with diethanolamine.

Dr. Hecht, the third principal reviewer, agreed with the proposed conclusions. He said that it would have been more satisfactory to have tested the diethanolamides in the absence of diethanolamine, although he realized that the strategy was to test the product as it actually is used. Dr. J.R. Bucher, NIEHS, agreed but stated that because this is a safety assessment issue, the determining factor was the diethanolamide as it is used in cosmetics. Dr. Hecht asked for some discussion of the significance of the liver neoplasms in a strain of mouse that already has a considerable spontaneous incidence of such neoplasms. Spontaneous incidences, along with the fact that no other substantial neoplasm responses were observed, suggest that coconut oil acid diethanolamine condensate is a weak carcinogen.

Dr. L. Loretz, The Cosmetic, Toiletry, and Fragrance Association (CTFA), said that there was inadequate documentation and analysis of the test materials, particularly when attributing neoplasm effects of the condensates to diethanolamine content. Furthermore, the test animals appeared to have ingested some of the material, and the inappropriate use of ethanol as the vehicle complicated interpretation of study results in that The International Agency for Research on Cancer (IARC) lists ethanol in beverages as a known human carcinogen. Finally, Dr. Loretz asked that the level of evidence for male mice, which was based on kidney neoplasms, be changed from *clear* to *some evidence of carcinogenic activity* because the response was limited to one species, one gender, and one dose and consisted primarily of benign neoplasms.

Dr. I. Russo moved that the Technical Report on coconut oil acid diethanolamine condensate be accepted with the revisions discussed and the conclusions as written with the addition of the word "marginal" before "increased" in the conclusion for female rats. Dr. Fischer seconded the motion. Dr. Goldsworthy moved that the motion be amended such that the last sentence of the conclusions for carcinogenicity be changed from "These increases were attributed to the concentration of free diethanolamine present as a contaminant" to "These increases were associated with the concentration of free diethanolamine present as a contaminant." Dr. Belinsky seconded the amendment, which was accepted by seven yes votes and one abstention (Dr. Bus). The amended motion was then accepted by seven yes votes and one abstention (Dr. Bus).

INTRODUCTION



n = 7, 9, 11, 13, or 15

COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

CAS No. 68603-42-9

Chemical Formula: $C_{(7+n)}H_{(15+2n)}O_3N$ Molecular Weight: 280-290

Synonyms: Cocamide DEA; cocamide diethanolamine; coconut oil diethanolamine; N,N-bis(hydroxyethyl)coco amides; N,N-bis(hydroxyethyl)coco fatty amides

Trade names: Clindrol 200CGN; Clindrol 202CGN; Clindrol Superamide 100CG; Comperlan KD; Comperlan LS; Comperlan PD; Conco Emulsifier K; Elromid KD 80; Empilan CDE; Ethylan LD; Ethylan A 15; Lauridit KDG; Marlamid D 1218; Monamid 150D; Monamid 150DB; Ninol 1281; Ninol 2012E; Ninol 2012 Extra; Ninol P 621; P and G Amide 72; Purton CFD; Schercomid CDA; Steinamid DC 2129; Steinamid DC 2129E; Varamide A 2; Varamide A 10; Varamide A 83; Witcamide 82; Witcamide 5133

CHEMICAL AND PHYSICAL PROPERTIES

Coconut oil is a mixture of fatty acids composed of approximately 48.2% lauric acid, 18% myristic acid, 8.5% palmitic acid, 8% caprylic (*n*-octanoic) acid, 7% capric (*n*-decanoic) acid, 6% oleic acid, 2.3% stearic acid, and 2% linoleic acid (*Source Book for Food Scientists,* 1978). Therefore, coconut oil acid diethanolamine condensate is a mixture of diethanolamides of these constituent fatty acids. Coconut oil acid diethanolamine condensate is available in several grades which differ on the basis of the molar ratio of coconut oil methyl esters and diethanolamine used during manufacture; the purest product is obtained with a molar ratio of 1:1. Free diethanolamine is present in the final product at concentrations ranging from 4% to 8.5%. Coconut oil acid diethanolamine condensate has a melting point range of 23° to 35° C; at room temperature and atmospheric pressure, most preparations are clear, amber-colored liquids with a faint coconut odor. Coconut oil acid diethanolamine condensate is soluble in water and produces a slightly alkaline aqueous solution (CTFA, 1985).

PRODUCTION, USE, AND HUMAN EXPOSURE

Coconut oil acid diethanolamine condensate is prepared by the condensation of coconut oil fatty acid methyl esters with diethanolamine at temperatures up to 170° C and in the presence of a catalyst (CTFA, 1985). Fatty acid diethanolamides, including coconut oil acid diethanolamine condensate, are widely used in cosmetics. Coconut oil acid diethanolamine condensate is present in approximately 584 cosmetic formulations of bath oils, shampoos, conditioners, lipsticks, and hair dyes. In these preparations, the concentration of diethanolamide may range from 1% to 25%. Noncosmetic applications include use as a surfactant in bar soaps, light-duty detergents, and dishwashing detergents and as a delinting agent for cottonseed (CTFA, 1985). The National Occupational

Exposure Survey (1981-1983) estimated that 589,000 workers were exposed to coconut oil acid diethanolamine annually (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

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

TOXICITY

Experimental Animals

In a 16-day study in male Sprague-Dawley rats, undiluted coconut oil acid diethanolamine condensate administered by gavage was slightly toxic and had an LD_{50} of 12.2 g/kg body weight; 10% or 12% dilutions had no effect. Dermal application of a 30% solution of coconut oil acid diethanolamine condensate to the shaved dorsal skin of a rabbit for 23 hours was judged to be moderately irritating (CTFA, 1985).

Humans

There have been several reports of skin irritation in humans exposed to consumer products where patch testing demonstrated that the offending substance was coconut oil acid diethanolamine condensate. The skin irritation was reported following exposure to a hand gel (Nurse, 1980), shampoos (De Groot *et al.*, 1987), hydraulic oil (Hindson and Lawlor, 1983), and handwashing liquids and barrier creams (Kanerva *et al.*, 1993; Pinola *et al.*, 1993).

CARCINOGENICITY

No information on the carcinogenicity of coconut oil acid diethanolamine condensate in experimental animals or epidemiology studies in humans was found in the literature.

GENETIC TOXICITY

Coconut oil acid diethanolamine condensate was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation (Zeiger *et al.*, 1988). No other published mutagenicity data for coconut oil acid diethanolamine condensate were identified.

STUDY RATIONALE

Coconut oil acid diethanolamine condensate is widely used in cosmetics, shampoos, soaps, and related consumer products to which humans are exposed extensively. These products are typically used on a daily basis for the majority of the human life span. Because of the lack of information about potential risks associated with long-term exposure, coconut oil acid diethanolamine condensate, lauric acid diethanolamine condensate, and oleic acid diethanolamine condensate were selected by the National Cancer Institute as representatives of the class of diethanolamides for evaluation of toxicity and carcinogenic potential. Because diethanolamine is a frequent contaminant of commercial preparations of diethanolamides, its toxicity and carcinogenic potential were also evaluated.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Coconut Oil Acid Diethanolamine Condensate

Coconut oil acid diethanolamine condensate was obtained from Henkel Corporation (Mauldin, SC) in one lot (1G01742286). 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 coconut oil acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a viscous yellow liquid, was identified as coconut oil acid diethanolamine condensate by infrared and nuclear magnetic resonance spectroscopy. The purity of lot 1G01742286 was determined by high-performance liquid chromatography and nitrosamine quantitation.

High-performance liquid chromatography indicated one major peak and 15 smaller peaks with areas of at least 0.5% relative to the major peak area. Lot 1G01742286 was composed primarily of diethanolamides of coconut oil acids, with unreacted diethanolamine, alkanolamides of unsaturated acids, and amine salts of the acids. The polar nitrosamine, *N*-nitrosodiethanolamine, was detected at a concentration of 219 ppb, which was considered consistent with the anticipated composition of commercial coconut oil acid diethanolamine condensate. No nonpolar nitrosamines were detected.

Stability studies of lot DS42578C0 of the bulk chemical were performed by the analytical chemistry laboratory on using nonaqueous titration of amine function of diethanolamine with perchloric acid. Coconut oil acid diethanolamine condensate showed some instability when stored in glass tubes for 2 weeks at 60° C. Stability was monitored during the 14-week and 2-year studies using high-performance liquid chromatography. 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 14 lots. The purity of the 95% ethanol used in these studies was monitored at the beginning and end of the 14-week studies and every 2 to 4 months during the 2-year studies using gas chromatography with a flame ionization detector. USP/NF ethanol reference standards were analyzed concomitantly. Purity of the bulk chemical ranged from 96.6% to 103.4% relative to that of the reference standard, except for one sample taken during the 2-year studies which measured 109.6%. This result was considered to be spurious because analysis of the same material approximately 2 months later indicated a relative purity of 101.1%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

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

The study laboratory performed stability studies of a 10 mg/mL formulation using high-performance liquid chromatography. When stored in sealed glass containers and protected from ultraviolet light, the stability of the dose formulation was confirmed for at least 28 days between –20° C and room temperature. When left open to air and light, the stability of coconut oil acid diethanolamine condensate was confirmed for 3 hours; however, a narrow-mouth bottle was suggested for storage during dose administration to decrease evaporation of the ethanol.

Periodic analyses of the dose formulations of coconut oil acid diethanolamine condensate were conducted at the study laboratory using high-performance liquid chromatography. 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, 13 of 15 dose formulations for rats and all 15 dose formulations for mice were within 10% of the target concentrations; two dose formulations for rats were remixed, and the remixes were determined to be within 10% of the target concentrations. All 48 dose formulations analyzed and used during the 2-year studies were within 10% of the target concentrations. In addition to dose formulation analyses prior to dosing, samples collected after dosing (animal room samples) were analyzed periodically. All animal room samples analyzed during the 14-week studies were within 10% of the target concentration. For the 2-year studies, 14 of 16 were within 10% of target concentration; two samples were 112% and 116% of target concentrations, apparently due to evaporation of the 95% ethanol from improperly sealed dosing bottles.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to coconut oil 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 to 17 days and were 6 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 special study rats received dermal applications of 0, 25, 50, 100, 200, or 400 mg coconut oil 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/kg 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. The animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded weekly. Details of the study design and animal maintenance are summarized in Table 1.

On days 4 and 24, blood was collected from the retroorbital sinus of clinical pathology study male and female rats from each dose 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, the rats 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 with no anticoagulant and allowed to clot, and the serum was obtained by centrifugation. The parameters measured are listed in Table 1. Hematology determinations, including erythrocyte and leukocyte counts, hemoglobin concentration, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration, were performed on a Serono-Baker 9000 hematology analyzer (Serono-Baker Diagnostics, Allentown, PA). Differential leukocyte counts were determined by light microscopy from blood smears stained with modified Wright-Giemsa. Smears made from blood samples stained with new methylene blue were examined microscopically for a quantitation of reticulocytes. Clinical chemistry parameters were measured with a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using commercially available reagents.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on rats administered 0, 100, 200, or 400 mg/kg and mice receiving 0, 200, 400, or 800 mg/kg. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology eval-

uations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study rats and 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 0 and 400 mg/kg core study rats and on 0 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 coconut oil acid diethanolamine condensate/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/kg 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 Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 to 14 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats 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 twice weekly. 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. 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. Clinical findings were recorded at the beginning of the study, and at 4-week intervals thereafter, and at the end of the study.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. 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 clitoral gland, forestomach, kidney, pancreas (males), preputial gland, prostate gland, skin (site of application), and thyroid gland (males) of rats and the bone marrow, kidney, liver, skin (site of application), spleen, and thyroid gland of 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 Coconut Oil 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 Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies	
Rats: 14 days (males) or 15 days (females) Mice: 16 days (males) or 17 days (females)	Rats: 11 days (males) or 12 days (females) Mice: 13 days (males) or 14 days (females)
Average Age When Studies Began	
6 weeks	6 weeks
Date of First Dose	
Rats: 10 February 1992 (males) 11 February 1992 (females) Mice: 12 February 1992 (males) 13 February 1992 (females)	Rats: 1 February 1993 (males) 2 February 1993 (females) Mice: 20 January 1993 (males) 21 January 1993 (females)
Duration of Dosing	
Five exposures per week for 14 weeks	Five exposures per week for 104 weeks (rats) or 104 to 105 weeks (mice)
Date of Last Dose	
Rats: 3 March 1992 (clinical pathology males) 4 March 1992 (clinical pathology females) 11 May 1992 (males) 12 May 1992 (females) Mice: 13 May 1992 (males) 14 May 1992 (females)	Rats: 27 January 1995 (males) 30 January 1995 (females) Mice: 17 January 1995 (males) 19 January 1995 (females)
Necropsy Dates	
Rats: 12 May 1992 (males) 13 May 1992 (females) Mice: 14 May 1992 (males) 15 May 1992 (females)	Rats: 30-31 January 1995 Mice: 16-20 January 1995
Average Age at Necropsy	
20 weeks	110 weeks (rats) or 111 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
Animals per Cage	
1	1

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

14-Week Studies	2-Year Studies
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 DuPont 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: 22.2°-23.9° C (rats) 20.6°-22.8° C (mice) Relative humidity: 38%-55% (rats) 41%-58% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 20.0°-23.9° C (rats) 20.6°-23.9° C (mice) Relative humidity: 33%-70% (rats) 30%-67% (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. Dosing volume varied with animal 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. Dosing volume varied with animal weight.	Rats: 0, 50, or 100 mg/kg (0, 85, or 170 mg/mL) in ethanol applied to shaved skin. Dosing volume varied with animal weight. Mice: 0, 100, or 200 mg/kg (0, 50, or 100 mg/mL) in ethanol applied to shaved skin. Dosing volume varied with animal weight.
Type and Frequency of Observation	
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly.	Observed twice daily; animals were weighed initially, weekly during weeks 1 through 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 the end of the study.
Method of Sacrifice	
Carbon dioxide asphyxiation	Same as 14-week studies

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

14-Week Studies	2-Year Studies
Necropsy Necropsy was performed on all core study rats and mice. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals.
Clinical Pathology Blood for hematology and clinical chemistry was collected from the retroorbital sinus of anesthetized supplemental rats on days 4 and 24 and from anesthetized core study rats at the end of the study. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, cholesterol, triglycerides, 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 (site of application) was examined in all core study groups, and the kidney was examined in core study male and female rats.	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. The following sperm motility parameters were evaluated: spermatid heads per gram of testis, spermatid heads per testis, spermatid count, and epididymal spermatozoal motility and concentration. The left cauda epididymis, epididymis, and testis were weighed. Vaginal samples for cytology evaluations were collected for 12 consecutive days prior to the end of the studies from all female rats in the 0, 100, 200, and 400 mg/kg groups and female mice in the 0, 200, 400, and 800 mg/kg groups. 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, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of $k=3$ was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are represented as 1−P with the letter N added (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 dosed and control groups in the analysis of continuous variables. Organ and body weight data, which historically 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 coconut oil 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 coconut oil 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 rats survived until the end of the study (Table 2). Final mean body weights and body weight gains of 200 and 400 mg/kg males and females were significantly less than those of the vehicle controls. Irritation of the skin at the site of application was observed in nearly all 200 and 400 mg/kg males and females and in two males and one female administered 100 mg/kg.

TABLE 2
Survival and Body Weights of Rats in the 14-Week Dermal Study of Coconut Oil 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	146 ± 3	352 ± 6	206 ± 6	
25	10/10	143 ± 4	342 ± 7	199 ± 6	97
50	10/10	144 ± 4	338 ± 5	194 ± 5	96
100	10/10	145 ± 3	338 ± 9	193 ± 8	96
200	10/10	143 ± 3	317 ± 7**	174 ± 6**	90
400	10/10	145 ± 4	283 ± 9**	137 ± 8**	80
Female					
0	10/10	117 ± 2	192 ± 3	76 ± 2	
25	10/10	115 ± 3	193 ± 4	78 ± 2	101
50	10/10	117 ± 3	188 ± 3	71 ± 3	98
100	10/10	117 ± 2	194 ± 6	77 ± 5	101
200	10/10	117 ± 2	177 ± 3*	60 ± 3**	92
400	10/10	115 ± 2	167 ± 4**	52 ± 3**	87

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

The hematology and clinical chemistry data for rats in the 14-week dermal study of coconut oil acid diethanolamine condensate are listed in Table F1. At week 14, a minimal microcytic, normochromic, nonresponsive anemia occurred in the 100 and 200 mg/kg females and 400 mg/kg males and females. The anemia also occurred in the 400 mg/kg males and females on day 24. The anemia was evidenced by decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts. Microcytic and normochromic erythrocytes were evidenced by decreased mean cell volumes and the lack of change in the mean cell hemoglobin concentration, respectively. The lack of an erythropoietic response was

evidenced by no change in the reticulocyte counts. Increased segmented neutrophil counts occurred in 400 mg/kg males and females at week 14 and in 400 mg/kg females on day 24.

There was an indication of altered lipid metabolism, evidenced by decreases of cholesterol and triglyceride concentrations. At all time points, the cholesterol concentration was decreased in 400 mg/kg male and female rats; on day 24 and at week 14, 100 mg/kg females and 200 mg/kg males and females were also affected. A transient decrease in cholesterol concentration also occurred in the 50 mg/kg female rats on day 24. Triglyceride concentration was decreased in 200 and 400 mg/kg male rats only at week 14. At week 14, there was a minimal concentration-related increase of serum albumin concentration in all treated groups of females and in 100 mg/kg or greater male rats; on day 24, increased albumin concentration occurred in the 400 mg/kg females. The increased albumin concentrations were reflected by increased total protein concentrations in 200 and 400 mg/kg female rats on day 24 and at week 14. There were minimal increases of urea nitrogen concentration that occurred in the 200 and 400 mg/kg female rats on day 24 and at week 14. At week 14, an increase in alanine aminotransferase activity occurred in 50 mg/kg or greater male rats. Additionally, alkaline phosphatase activity was increased in 400 mg/kg males. Increased activities of these enzymes could indicate altered hepatocellular integrity or cholestasis. However, the female rats were not affected, and other biomarkers of hepatocellular leakage and/or function (serum sorbitol dehydrogenase activity and bile salt concentration) were not affected.

Left epididymis weights of 200 and 400 mg/kg males were significantly less than those of the vehicle controls, but this was most likely secondary to decreased mean body weights in these groups (Table H1). Estrous cycle lengths of dosed females were similar to those of the vehicle controls (Table H2).

Kidney weights of females administered 50 mg/kg or greater were significantly greater than those of the vehicle control group (Table G1).

The incidences of epidermal hyperplasia in all dosed groups of males and in females administered 50 mg/kg or greater were significantly greater than those in the vehicle controls (Table 3). Compared to the vehicle controls, the incidences of sebaceous gland hyperplasia were significantly increased in males administered 50 mg/kg or greater and in females administered 100 mg/kg or greater. The incidences of chronic active inflammation in 100, 200, and 400 mg/kg males and females significantly exceeded the vehicle control incidences. The incidences of parakeratosis and ulcer in 200 and 400 mg/kg males and females were significantly greater than in the vehicle controls. The severities of these skin lesions generally increased with increasing dose in males and females.

Males in the 400 mg/kg group had a significantly lower incidence of minimal renal tubule regeneration than did the vehicle controls. The incidences of renal tubule regeneration in 100, 200, and 400 mg/kg females were significantly greater than the vehicle control incidence, and the severities were greater at 200 and 400 mg/kg.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male						
Skin, Site of Application[a]	10	10	10	10	10	10
Epidermis, Hyperplasia[b]	0	7** (1.1)[c]	10** (1.4)	10** (2.3)	10** (2.9)	10** (3.0)
Sebaceous Gland, Hyperplasia	0	0	6** (1.0)	9** (1.7)	10** (3.0)	10** (3.0)
Inflammation, Chronic, Active	0	0	0	8** (1.0)	10** (1.9)	10** (2.9)
Parakeratosis	0	0	0	3 (1.0)	9** (3.1)	10** (3.9)
Ulcer	0	0	0	1 (1.0)	6** (3.2)	7** (4.0)
Kidney	10	10	10	10	10	10
Renal Tubule, Regeneration	9 (1.0)	9 (1.2)	9 (1.1)	9 (1.1)	5 (1.0)	3** (1.0)
Female						
Skin, Site of Application	10	10	10	10	10	10
Epidermis, Hyperplasia	0	2 (1.0)	10** (1.5)	10** (1.8)	10** (3.0)	10** (3.0)
Sebaceous Gland, Hyperplasia	0	0	0	7** (1.3)	10** (3.0)	10** (3.0)
Inflammation, Chronic Active	0	0	0	9** (1.0)	10** (2.8)	10** (3.0)
Parakeratosis	0	0	0	0	10** (3.4)	10** (4.0)
Ulcer	0	0	0	0	10** (3.8)	10** (3.9)
Kidney	10	10	10	10	10	10
Renal Tubule, Regeneration	3 (1.0)	5 (1.0)	7 (1.0)	10** (1.0)	10** (1.6)	10** (2.0)

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

Dose Selection Rationale: Doses of 200 or 400 mg/kg were associated with reduced mean body weights, mild anemia, and significantly increased incidences and severities of lesions of the skin at the site of application. Therefore, these doses were considered inappropriate for a 2-year study. At 100 mg/kg, the incidences of skin lesions, especially ulceration, were less than at 200 mg/kg, and in general, the severities were minimal to mild. Therefore, 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, therefore, 50 mg/kg was selected as the low dose.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 1). Survival rates of dosed male and female rats were similar to those of the vehicle controls.

Body Weights and Clinical Findings

The mean body weights of dosed male and female rats were similar to those of the vehicle controls throughout most of the study (Tables 5 and 6 and Figure 2). The only clinical finding attributed to dosing was irritation of the skin at the site of application in 100 mg/kg females.

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

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Animals initially in study	50	50	50
Accidental death[a]	1	0	0
Moribund	28	27	25
Natural deaths	13	11	14
Animals surviving to study termination	8	12	11
Percent probability of survival at end of study[b]	16	24	22
Mean survival (days)[c]	594	633	629
Survival analysis[d]	P=0.324N	P=0.270N	P=0.350N
Female			
Animals initially in study	50	50	50
Moribund	7	15	10
Natural deaths	15	11	18
Animals surviving to study termination	28	24	22[e]
Percent probability of survival at end of study	56	48	44
Mean survival (days)	683	638	621
Survival analysis	P=0.142	P=0.350	P=0.165

[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 comparison (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.
[e] Includes one animal that died during the last week of the study

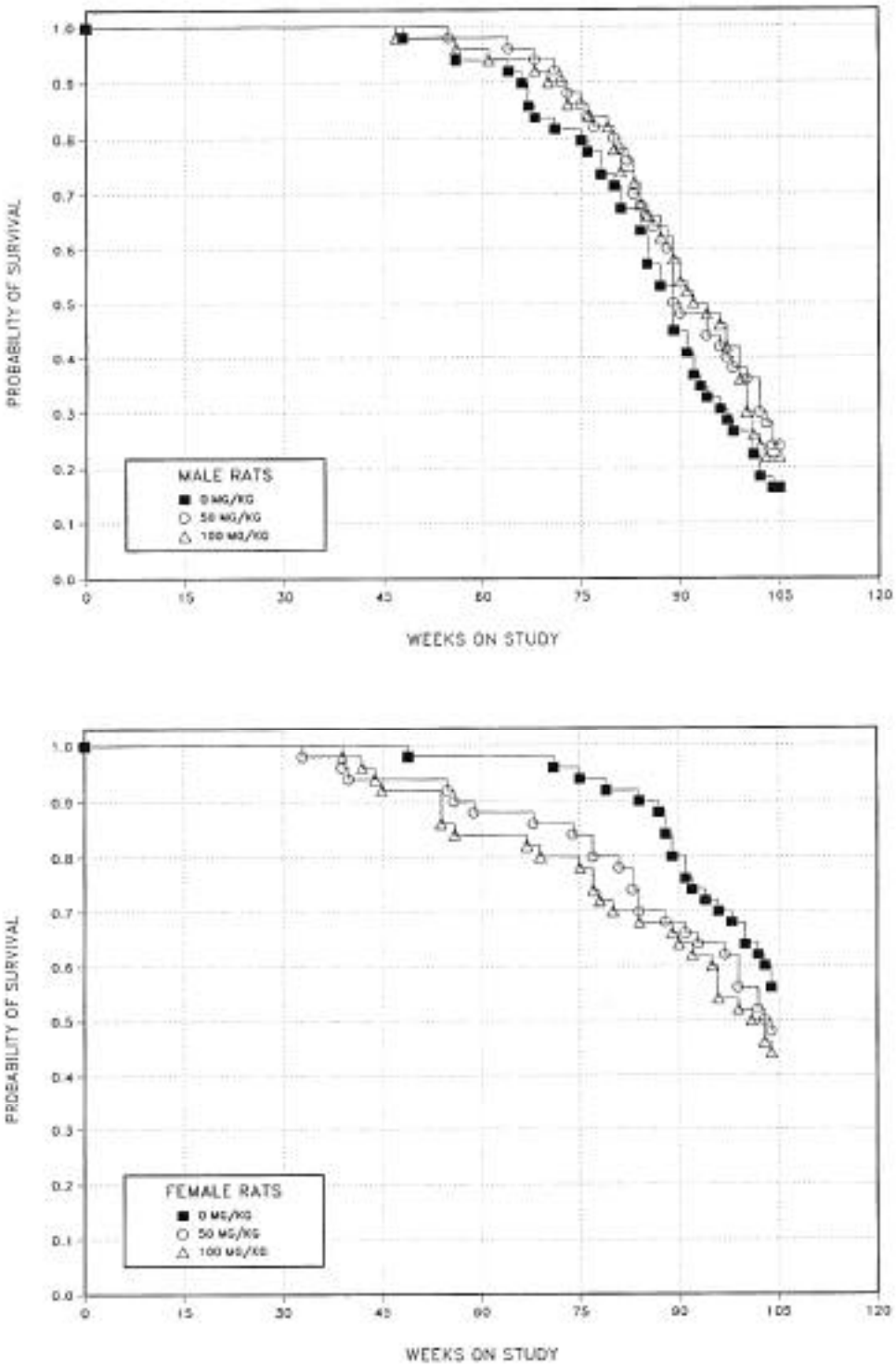


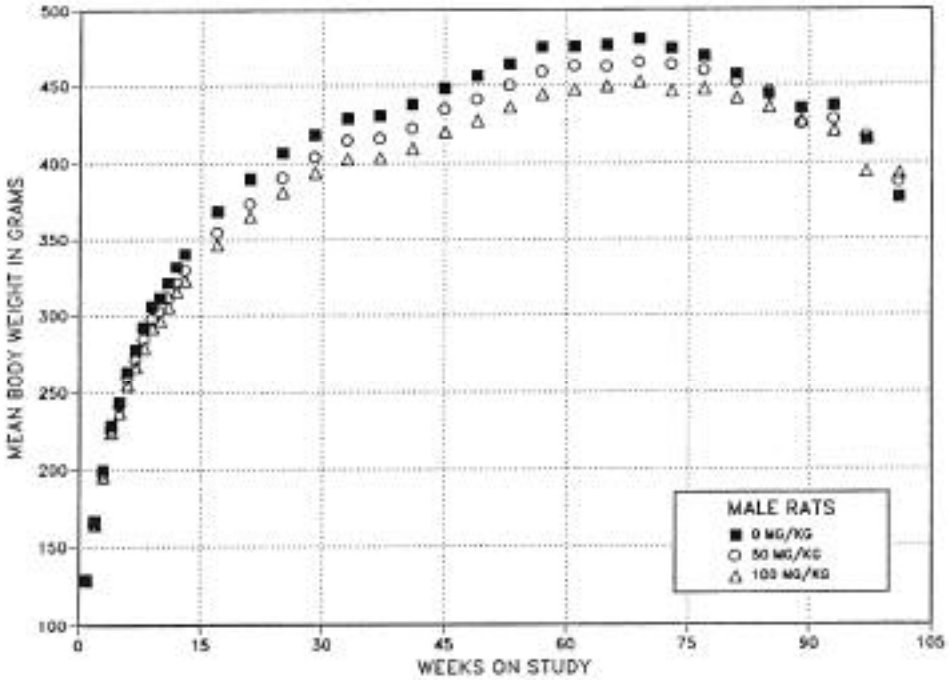
Figure 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Coconut Oil Acid Diethanolamine Condensate Dermally for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Coconut Oil 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	129	50	129	100	50	129	100	50
2	167	50	165	99	50	165	99	50
3	200	50	197	99	50	196	98	50
4	229	50	226	99	50	224	98	50
5	244	50	242	99	50	237	97	50
6	263	50	259	99	50	255	97	50
7	278	50	271	98	50	267	96	50
8	292	50	285	98	50	279	96	50
9	306	50	298	97	50	292	96	50
10	311	50	303	97	50	296	95	50
11	321	50	312	97	50	306	95	50
12	332	50	321	97	50	315	95	50
13	340	50	330	97	50	323	95	50
17	368	49	355	96	50	347	94	50
21	390	49	374	96	50	365	94	50
25	407	49	391	96	50	381	94	50
29	418	49	404	97	50	394	94	50
33	429	49	415	97	50	403	94	50
37	430	49	416	97	50	404	94	50
41	438	49	422	97	50	410	94	50
45	448	49	435	97	50	420	94	50
49	456	48	441	97	50	427	94	49
53	464	48	450	97	50	436	94	49
57	475	46	459	97	49	444	94	48
61	475	46	463	97	49	447	94	47
65	476	45	462	97	48	450	94	47
69	481	41	465	97	47	452	94	46
73	474	40	463	98	45	446	94	45
77	469	38	460	98	42	448	95	42
81	457	34	452	99	40	442	97	39
85	444	31	446	101	34	436	98	34
89	435	26	425	98	30	426	98	31
93	436	18	428	98	24	421	96	25
97	415	15	417	101	21	394	95	23
101	378	13	388	103	18	393	104	14
Mean for weeks								
1-13	262		257	98		253	97	
14-52	420		406	97		395	94	
53-101	452		444	99		433	96	

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

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	106	50	106	100	50	106	100	50
2	123	50	122	99	50	123	100	50
3	135	50	134	100	50	135	100	50
4	149	50	148	99	50	148	100	50
5	156	50	155	99	50	155	99	50
6	164	50	162	99	50	162	99	50
7	169	50	166	98	50	166	98	50
8	175	50	172	98	50	172	98	50
9	180	50	177	98	50	175	97	50
10	183	50	179	98	50	177	97	50
11	187	50	184	98	50	181	97	50
12	191	50	186	98	50	185	97	50
13	193	50	189	98	50	187	97	50
17	204	50	201	98	50	199	98	50
21	208	50	205	99	50	203	97	50
25	216	50	213	99	50	211	97	50
29	226	50	221	98	50	220	97	50
33	233	50	227	98	49	226	97	50
37	237	50	231	97	49	227	96	50
41	246	50	240	98	47	233	95	49
45	254	50	248	97	47	245	97	47
49	263	50	258	98	47	254	97	46
53	274	49	267	98	47	262	96	46
57	283	49	275	97	45	274	97	42
61	286	49	280	98	44	279	98	42
65	291	49	285	98	44	281	97	42
69	296	49	290	98	43	287	97	41
73	297	48	293	99	43	291	98	40
77	301	47	294	98	42	290	96	39
81	304	46	296	97	40	297	98	35
85	303	45	301	99	35	296	98	34
89	305	42	304	100	34	293	96	34
93	307	37	297	97	33	291	95	31
97	307	35	291	95	32	289	94	27
101	312	32	295	95	28	276	88	26
Mean for weeks								
1-13	162		160	99		159	98	
14-52	232		227	98		224	97	
53-101	297		290	98		285	96	



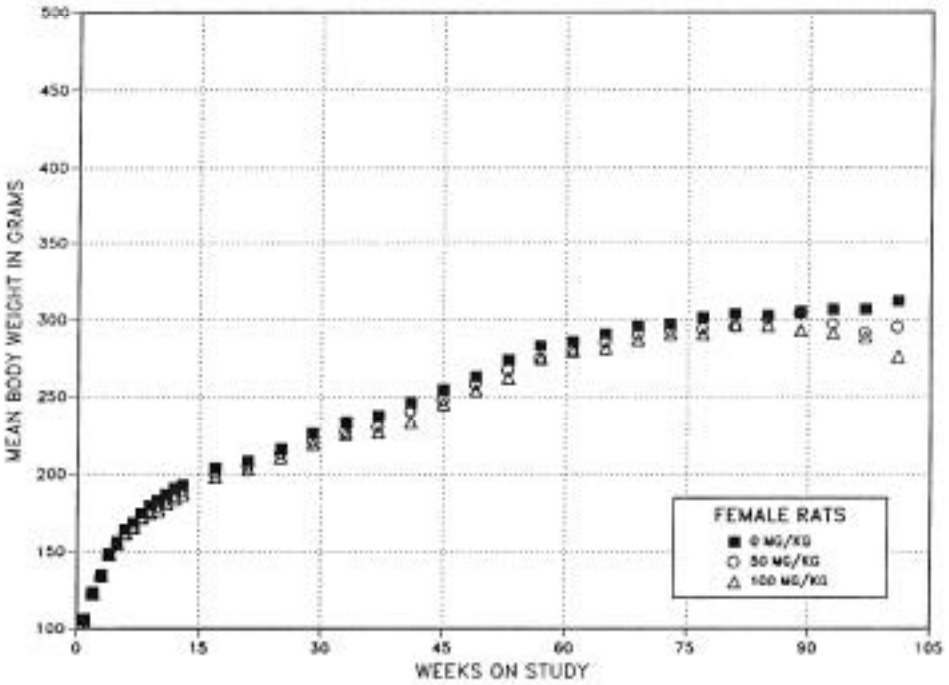


Figure 2
Growth Curves for Male and Female Rats Administered Coconut Oil Acid Diethanolamine Condensate Dermally for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the skin, kidney, forestomach, and pancreas. 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 mention in this section are presented in Appendix A for male rats and Appendix B for female rats.

Skin: No neoplasms of the skin were attributed to treatment with coconut oil acid diethanolamine condensate. Incidences of squamous cell papilloma, keratoacanthoma, trichoepithelioma, basal cell adenoma, or carcinoma (combined) were significantly decreased in 100 mg/kg male rats (6/50, 9/50, 1/50; Table A3). Incidences of epidermal hyperplasia, sebaceous gland hyperplasia, parakeratosis, and hyperkeratosis in all dosed groups were significantly greater than those in the vehicle control groups (Tables 7, A5, and B5). The severities of these lesions generally increased with increasing dose and ranged from minimal to mild. No skin lesions were observed at the site of application in vehicle control males. Females in the 100 mg/kg group had a significantly greater incidence of ulceration at the site of application than did the vehicle controls. Epidermal hyperplasia and sebaceous gland hyperplasia consisted of increased numbers of cells in the epidermis or sebaceous glands. The epidermis and sebaceous glands were thickened because of the hyperplasia. Hyperkeratosis was characterized by increased keratin on the surface.

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

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Number Examined Microscopically	50	50	50
Epidermis, Hyperplasia[a]	0	46** (1.5)[b]	50** (2.4)
Sebaceous Gland, Hyperplasia	0	45** (1.5)	50** (2.2)
Parakeratosis	0	9** (1.2)	28** (1.9)
Hyperkeratosis	0	36** (1.4)	48** (1.9)
Female			
Number Examined	50	50	50
Epidermis, Hyperplasia	3 (2.3)	46** (1.7)	50** (2.3)
Sebaceous Gland, Hyperplasia	2 (1.5)	46** (1.7)	49** (2.0)
Parakeratosis	1 (1.0)	11** (1.2)	23** (2.0)
Hyperkeratosis	3 (1.3)	45** (1.6)	47** (1.7)
Ulcer	2 (2.5)	0	9* (2.2)

* 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

Kidney: Initially, single sections of each kidney were evaluated. Incidences of renal tubule hyperplasia in dosed females were significantly greater than those of the vehicle controls, and the incidence of renal tubule adenoma in 50 mg/kg males was marginally increased (Tables 8, A3, and B5). The incidences of renal tubule adenoma in all groups of males and of renal tubule carcinoma in 50 mg/kg females exceeded the historical control ranges (Tables 8, A4, and B4). An extended evaluation of the kidney revealed additional renal tubule adenomas in vehicle control and dosed males, and renal tubule adenomas and/or carcinomas in dosed females. Additional incidences of renal tubule hyperplasia were observed in all groups. When the single and step sections were combined, the incidences of renal tubule hyperplasia in dosed females and of renal tubule adenoma or carcinoma (combined) in 50 mg/kg females were significantly greater than those of the controls.

Incidences of chronic nephropathy were similar between vehicle control and dosed groups of male and female rats (Tables 8, A5, and B5); however, the severity of nephropathy increased with increasing dose in female rats.

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control		50 mg/kg		100 mg/kg	
Male						
Number Examined Microscopically	50		50		50	
Single Sections (Standard Evaluation)						
Chronic Nephropathy	49	(2.8)	50	(2.7)	49	(2.7)
Renal Tubule Hyperplasia[a]	13	(2.2)[b]	13	(1.9)	15	(2.3)
Renal Tubule Adenoma[c]	3		6		3	
Renal Tubule Carcinoma	0		1		0	
Renal Tubule Adenoma or Carcinoma[d]	3		7		3	
Step Sections (Extended Evaluation)						
Renal Tubule Hyperplasia	8		8		14	
Renal Tubule Adenoma	8		8		8	
Renal Tubule Carcinoma	0		1		0	
Renal Tubule Adenoma or Carcinoma	8		9		8	
Single and Step Sections (Combined)						
Renal Tubule Hyperplasia	16		17		23	
Renal Tubule Adenoma	11		10		10	
Renal Tubule Carcinoma	0		2		0	
Renal Tubule Adenoma or Carcinoma	11		11		10	

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Female			
Number Examined Microscopically	50	50	50
Single Sections (Standard Evaluation)			
Chronic Nephropathy	47 (1.6)	46 (2.1)	46 (2.7)
Renal Tubule Hyperplasia	2 (2.0)	8* (2.5)	15** (1.9)
Renal Tubule Carcinoma[e]	0	2	0
Step Sections (Extended Evaluation)			
Renal Tubule Hyperplasia	2 (1.0)	2 (2.0)	4 (2.8)
Renal Tubule Adenoma	0	2	1
Renal Tubule Carcinoma	0	1	0
Renal Tubule Adenoma or Carcinoma	0	3	1
Single and Step Sections (Combined)			
Renal Tubule Hyperplasia	4 (1.5)	10* (2.4)	17** (2.2)
Renal Tubule Adenoma	0	2	1
Renal Tubule Carcinoma	0	2	0
Renal Tubule Adenoma or Carcinoma			
Overall rate[f]	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate[g]	0.0%	10.6%	2.8%
Terminal rate[h]	0/28 (0%)	3/24 (13%)	1/22 (5%)
First incidence (days)	—[j]	719	728 (T)
Poly-3 test[i]	P=0.293	P=0.045	P=0.464

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP dermal studies with ethanol vehicle controls (mean ± standard deviation): 8/302 (2.7% ± 3.0%); range, 0%-6%
[d] Historical incidence: 9/302 (3.0% ± 3.5%); range, 0%-8%
[e] Historical incidence: 0/301
[f] Number of animals with neoplasm per number of animals with kidney examined microscopically
[g] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[h] Observed incidence at terminal kill
[i] 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.
[j] Not applicable, no neoplasms in animal group

Forestomach: The incidences of chronic active inflammation (vehicle control, 1/50; 50 mg/kg, 3/50; 100 mg/kg,10/50), epithelial hyperplasia (2/50, 5/50, 13/50), and epithelial ulcer (1/50, 3/50, 11/50) were significantly increased in the forestomach of 100 mg/kg females (Table B5). The severities of these lesions were similar among all groups (inflammation: 3.0, 2.3, 2.8; epithelial hyperplasia: 2.5, 2.6, 2.9; epithelial ulcer: 4.0, 4.0, 3.5).

Pancreas: The incidence of pancreatic acinar atrophy in 100 mg/kg male rats was significantly greater than that in the vehicle controls (11/50, 22/50, 25/50; Table A5).

MICE

14-WEEK STUDY

All mice survived until the end of the study (Table 9). Final mean body weights and body weight gains of dosed males and females were similar to those of the vehicle controls. The only treatment-related clinical finding was irritation of the skin at the site of application in all males and females administered 800 mg/kg.

The absolute and relative liver and right kidney weights of 800 mg/kg males and females and the absolute and relative liver weights of 400 mg/kg females were significantly greater than those of the vehicle controls (Table G2). The absolute and relative lung weights of 800 mg/kg females were also significantly greater than those of the vehicle controls.

The epididymal spermatozoal concentration of 800 mg/kg males was significantly greater than that of the vehicle controls (Table H3). Estrous cycle lengths of dosed females were similar to that of the vehicle controls (Table H4).

TABLE 9
Survival and Body Weights of Mice in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	24.4 ± 0.2	37.8 ± 1.2	13.4 ± 1.1	
50	10/10	24.4 ± 0.2	36.0 ± 0.5	11.7 ± 0.4	95
100	10/10	24.4 ± 0.2	36.3 ± 0.7	11.9 ± 0.7	96
200	10/10	24.1 ± 0.3	37.2 ± 1.0	13.1 ± 1.0	99
400	10/10	24.8 ± 0.3	37.1 ± 1.2	12.4 ± 1.1	98
800	10/10	24.6 ± 0.2	37.4 ± 1.1	12.8 ± 1.0	99
Female					
0	10/10	20.2 ± 0.4	31.0 ± 1.0	10.8 ± 0.7	
50	10/10	19.7 ± 0.2	31.2 ± 0.6	11.5 ± 0.5	101
100	10/10	20.1 ± 0.4	32.7 ± 1.2	12.6 ± 1.0	105
200	10/10	20.2 ± 0.4	29.4 ± 0.4	9.2 ± 0.3	95
400	10/10	20.2 ± 0.3	29.9 ± 0.5	9.8 ± 0.4	96
800	10/10	20.2 ± 0.2	29.4 ± 0.5	9.2 ± 0.4	95

[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group are not significant by Williams' or Dunnett's test.

In all dosed groups, the incidences of epidermal hyperplasia and sebaceous gland hyperplasia at the site of application were significantly greater than those in vehicle controls, and the severities of these lesions generally increased with increasing dose (Table 10). The incidences of chronic active inflammation of the skin in 200, 400, and 800 mg/kg males and females were significantly greater than those in the vehicle controls, and the severities were increased in the 800 mg/kg groups. Compared to the vehicle controls, the incidences of parakeratosis in 200, 400, and 800 mg/kg males and 400 and 800 mg/kg females were significantly greater than those in the vehicle controls. The incidences of skin ulceration in 800 mg/kg males and females were significantly greater than the vehicle control incidences.

TABLE 10
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
Number Examined	10	10	10	10	10	10
Microscopically						
Epidermis, Hyperplasia[a]	0	7** (1.0)[b]	9** (1.1)	10** (1.8)	8** (1.8)	10** (2.2)
Sebaceous Gland, Hyperplasia	0	7** (1.1)	10** (1.2)	10** (1.5)	9** (1.8)	10** (2.3)
Inflammation, Chronic, Active	0	0	0	8** (1.0)	7** (1.0)	9** (1.4)
Parakeratosis	0	0	0	5* (1.0)	7** (1.0)	9** (1.6)
Ulcer	0	0	0	1 (1.0)	4* (1.0)	6** (1.2)
Female						
Number Examined	10	10	10	10	10	10
Microscopically						
Epidermis, Hyperplasia	0	4* (1.0)	9** (1.1)	10** (1.6)	10** (1.7)	10** (2.7)
Sebaceous Gland, Hyperplasia	0	4* (1.3)	10** (1.1)	10** (1.8)	10** (2.0)	10** (3.4)
Inflammation, Chronic, Active	0	0	1 (1.0)	6** (1.0)	7** (1.0)	9** (1.8)
Parakeratosis	0	0	0	2 (1.0)	5* (1.0)	7** (1.7)
Ulcer	0	0	0	0	0	5* (1.0)

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

Dose Selection Rationale: Exposure to coconut oil acid diethanolamine condensate for 14 weeks produced only a minimal toxic response in mice except in the skin at the site of application. The incidences of chronic active inflammation as well as several other skin lesions were significantly increased at doses of 200 mg/kg and greater in both male and female mice. The incidences of ulceration were increased in males exposed to 400 and 800 mg/kg and in females exposed to 800 mg/kg. Therefore, 400 and 800 mg/kg were considered inappropriate for a 2-year study. However, ulceration was present in only one 200 mg/kg male and no females, and the severities of these lesions in all affected groups were minimal to mild. Below 200 mg/kg, the incidences of skin lesions decreased markedly with a minor difference in response between 50 and 100 mg/kg. Therefore, 200 mg/kg was selected as the high dose and 100 mg/kg as the low dose for the 2-year mouse study.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). The survival of dosed males and 100 mg/kg females was similar to that of the vehicle controls. Survival of the 200 mg/kg group of female mice was reduced compared to the vehicle control group, but the difference was not significant.

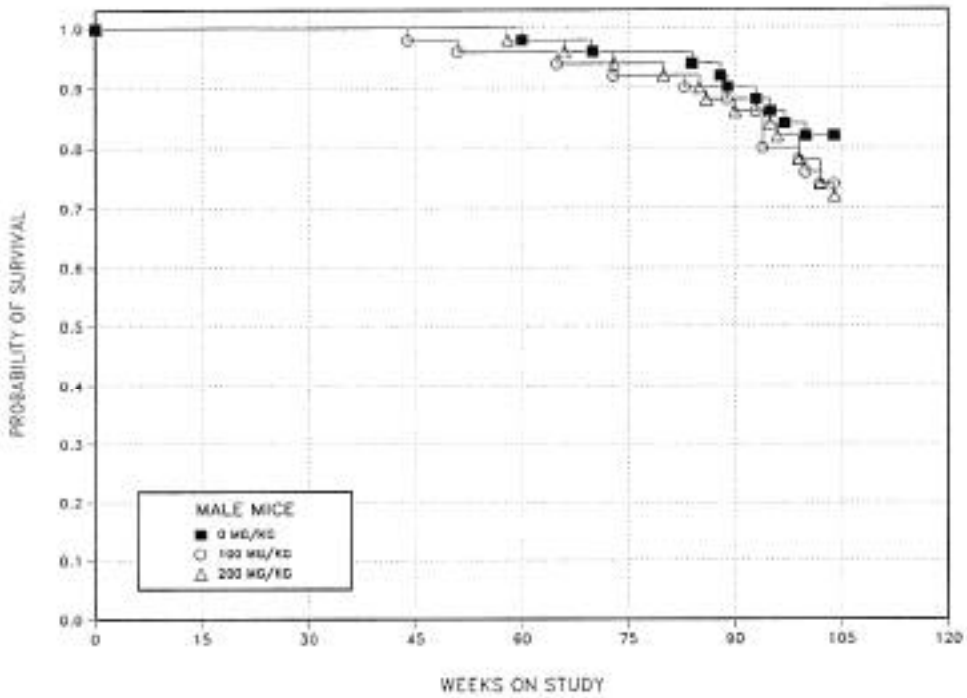
Body Weights and Clinical Findings

Mean body weights of dosed males were similar to those of the vehicle controls throughout most of the study; those of 100 and 200 mg/kg females were less than those of the vehicle controls from weeks 93 and 77, respectively (Figure 4 and Tables 12 and 13). The only treatment-related clinical finding was irritation of the skin at the site of application in males that received 200 mg/kg.

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

	Vehicle Control	100 mg/kg	200 mg/kg
Male			
Animals initially in study	50	50	50
Moribund	5	7	7
Natural deaths	4	6	7
Animals surviving to study termination	41	37	36
Percent probability of survival at end of study[a]	82	74	72
Mean survival (days)[b]	704	688	695
Survival analysis[c]	P=0.318	P=0.456	P=0.356
Female			
Animals initially in study	50	50	50
Moribund	11	11	15
Natural deaths	4	3	9
Animals surviving to study termination	35	36[d]	26
Percent probability of survival at end of study	70	72	52
Mean survival (days)	700	696	665
Survival analysis	P=0.056	P=1.000N	P=0.070

[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 columns. A lower mortality in a dose group is indicated by N.
[d] Includes one animal that died during the last week of study



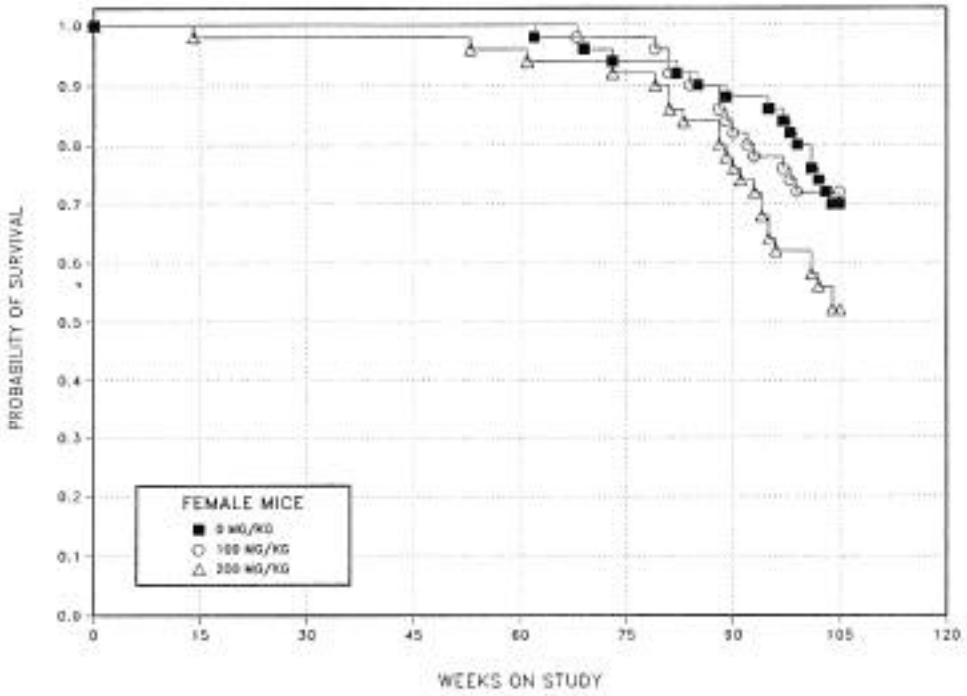


Figure 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Coconut Oil Acid Diethanolamine Condensate Dermally for 2 Years

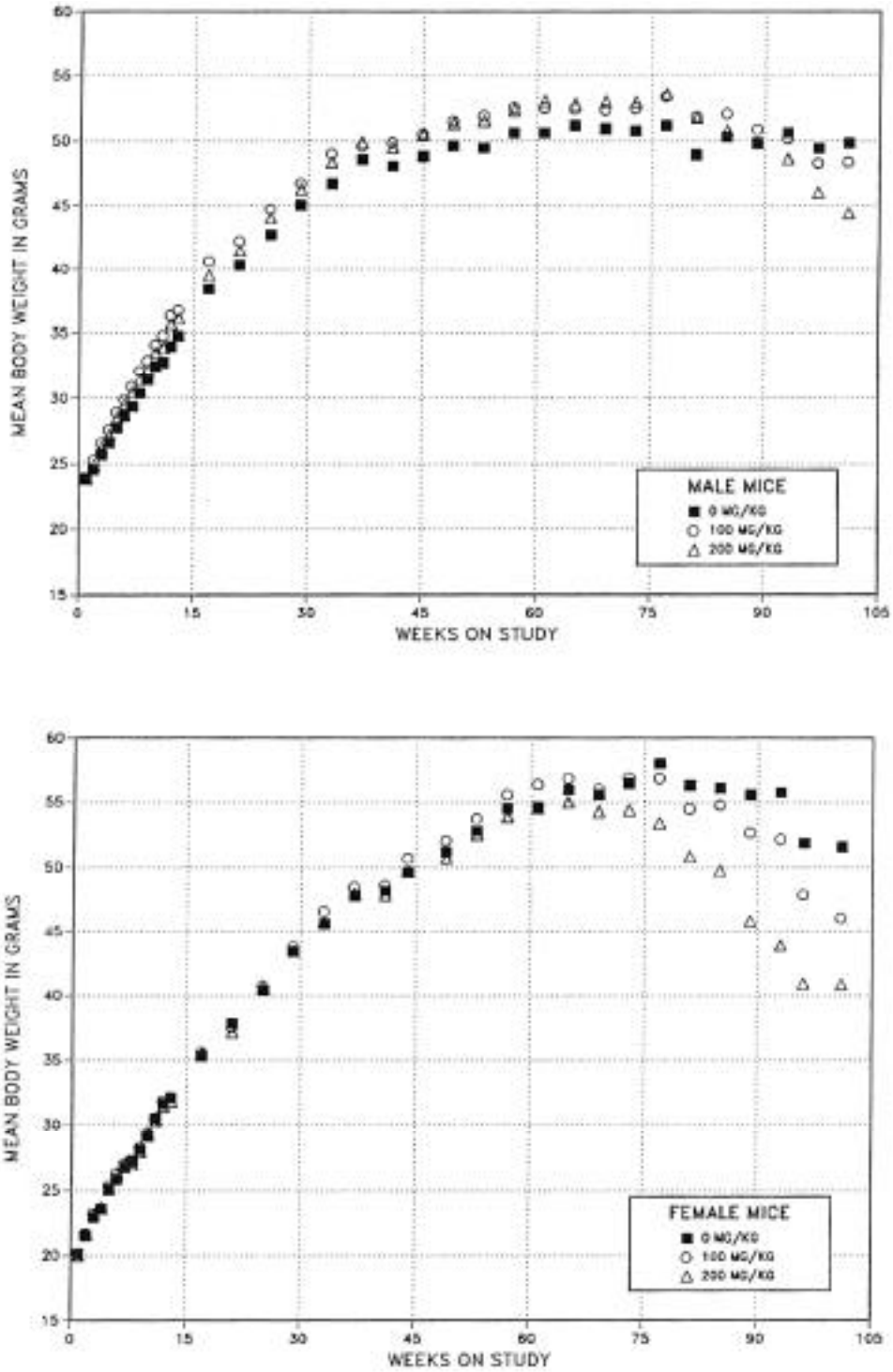


Figure 4
Growth Curves for Male and Female Mice Administered Coconut Oil Acid Diethanolamine Condensate Dermally for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Coconut Oil 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	23.9	50	23.8	100	50	23.9	100	50
2	24.6	50	25.2	102	50	24.9	101	50
3	25.7	50	26.6	104	50	26.2	102	50
4	26.6	50	27.6	104	50	27.2	102	50
5	27.8	50	28.9	104	50	28.5	103	50
6	28.7	50	29.9	104	50	29.6	103	50
7	29.4	50	30.9	105	50	30.4	103	50
8	30.4	50	32.1	106	50	31.4	103	50
9	31.4	50	32.8	105	50	32.1	102	50
10	32.4	50	34.0	105	50	33.5	103	50
11	32.7	50	34.8	106	50	33.8	103	50
12	33.9	50	36.3	107	50	35.7	105	50
13	34.7	50	36.8	106	50	36.1	104	50
17	38.4	50	40.6	106	50	39.5	103	50
21	40.3	50	42.2	105	50	41.5	103	50
25	42.7	50	44.7	105	50	44.0	103	50
29	45.0	50	46.7	104	50	46.3	103	50
33	46.7	50	49.0	105	50	48.4	104	50
37	48.5	50	49.6	102	50	49.9	103	50
41	48.1	50	49.9	104	50	49.5	103	50
45	48.8	50	50.5	104	49	50.5	104	50
49	49.6	50	51.5	104	49	51.3	103	50
53	49.5	50	51.9	105	48	51.5	104	50
57	50.6	50	52.5	104	48	52.3	103	50
61	50.6	49	52.5	104	48	53.0	105	49
65	51.2	49	52.4	102	48	52.8	103	49
69	50.9	49	52.3	103	47	53.0	104	48
73	50.7	48	52.5	104	47	53.0	105	47
77	51.2	48	53.4	104	46	53.6	105	47
81	48.9	48	51.8	106	46	51.8	106	46
85	50.3	47	52.1	104	45	50.8	101	46
89	49.8	46	50.9	102	44	49.9	100	44
93	50.6	44	50.2	99	44	48.6	96	43
97	49.4	43	48.3	98	40	46.0	93	41
101	49.8	41	48.4	97	38	44.4	89	39
Mean for weeks								
1-13	29.4		30.7	104		30.3	103	
14-52	45.3		47.2	104		46.8	103	
53-101	50.3		51.5	102		50.8	101	

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Coconut Oil 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	20.1	50	20.2	101	50	20.0	100	50
2	21.5	50	21.7	101	50	21.7	101	50
3	22.9	50	23.2	101	50	23.2	101	50
4	23.5	50	23.6	100	50	23.7	101	50
5	25.0	50	25.3	101	50	25.1	100	50
6	25.8	50	26.3	102	50	26.2	102	50
7	26.7	50	27.0	101	50	26.9	101	50
8	27.2	50	27.1	100	50	27.0	99	50
9	28.1	50	28.3	101	50	28.0	100	50
10	29.1	50	29.4	101	50	29.3	101	50
11	30.5	50	30.5	100	50	30.3	99	50
12	31.6	50	31.8	101	50	31.4	99	50
13	32.1	50	32.2	100	50	31.8	99	50
17	35.3	50	35.6	101	50	35.5	101	49
21	37.9	50	37.5	99	50	37.2	98	49
25	40.4	50	40.7	101	50	40.6	101	49
29	43.4	50	43.8	101	50	43.5	100	49
33	45.6	50	46.5	102	50	45.8	100	49
37	47.8	50	48.5	102	50	48.0	100	49
41	48.1	50	48.6	101	50	47.8	99	49
44	49.6	50	50.7	102	50	49.7	100	49
49	51.2	50	52.1	102	50	50.7	99	49
53	52.8	50	53.8	102	50	52.5	99	49
57	54.5	50	55.6	102	50	53.9	99	48
61	54.6	50	56.4	103	50	54.5	100	48
65	56.0	49	56.8	101	50	55.0	98	47
69	55.6	49	56.0	101	49	54.3	98	47
73	56.5	48	56.9	101	49	54.4	96	47
77	58.0	47	56.8	98	49	53.4	92	46
81	56.3	47	54.5	97	48	50.9	90	45
85	56.1	46	54.8	98	45	49.8	89	42
89	55.6	44	52.7	95	43	45.8	82	40
93	55.8	44	52.2	94	40	43.9	79	37
96	51.9	43	47.9	92	39	40.9	79	32
101	51.6	40	46.0	89	36	40.9	79	31
Mean for weeks								
1-13	26.5		26.7	101		26.5	100	
14-52	44.4		44.9	101		44.3	100	
53-101	55.0		53.9	98		50.0	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, kidney, skin, 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: Dosed male and female mice had significantly greater incidences of hepatic neoplasms than the vehicle controls (Tables 14, C3, and D3). These neoplasms included hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma (males). The incidences of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) in 200 mg/kg males and 100 and 200 mg/kg females exceeded the historical control ranges (Tables 14, C4a, and D4). The incidences of eosinophilic foci in dosed groups of males were increased relative to that in the vehicle controls; the incidences in dosed females were also increased, but the differences from the vehicle controls were not significant (Tables 14, C5, and D5).

There was a morphologic continuum from adenoma to carcinoma, with less differentiation and typical trabecular formations in the carcinomas. Carcinomas were often a centimeter or more in diameter, whereas adenomas were generally smaller and more discrete. Carcinomas metastasized to the lung in a few males and females. Adenomas, carcinomas, and hepatoblastomas displaced normal liver parenchyma, and none contained normal lobular architecture. Hepatoblastomas were characterized by well-demarcated focal areas composed of bundles of deeply basophilic, spindle-shaped cells.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	100 mg/kg	200 mg/kg
Male			
Number Examined Microscopically	50	50	50
Eosinophilic Focus[a]	20	29*	31*
Hepatocellular Adenoma, Multiple	11	24	41
Hepatocellular Adenoma (includes multiple)[b]			
Overall rate[c]	22/50 (44%)	35/50 (70%)	45/50 (90%)
Adjusted rate[d]	46.2%	75.4%	91.4%
Terminal rate[e]	18/41 (44%)	29/37 (78%)	34/36 (94%)
First incidence (days)	612	507	401
Poly-3 test[f]	P<0.001	P=0.002	P<0.001
Hepatocellular Carcinoma, Multiple	5	2	8
Hepatocellular Carcinoma (includes multiple)[g]			
Overall rate	12/50 (24%)	12/50 (24%)	20/50 (40%)
Adjusted rate	25.4%	26.2%	43.0%
Terminal rate	9/41 (22%)	7/37 (19%)	15/36 (42%)
First incidence (days)	584	576	456
Poly-3 test	P=0.041	P=0.561	P=0.055
Hepatocellular Adenoma or Carcinoma (includes multiple)			
Overall rate	28/50 (56%)	39/50 (78%)	47/50 (94%)
Adjusted rate	58.0%	82.4%	95.3%
Terminal rate	22/41 (54%)	30/37 (81%)	34/36 (94%)
First incidence (days)	584	507	401
Poly-3 test	P<0.001	P=0.007	P<0.001
Hepatoblastoma, Multiple	1	0	0
Hepatoblastoma (includes multiple)[h]			
Overall rate	1/50 (2%)	1/50 (2%)	10/50 (20%)
Adjusted rate	2.1%	2.2%	22.1%
Terminal rate	0/41 (0%)	0/37 (0%)	8/36 (22%)
First incidence (days)	664	507	692
Poly-3 test	P<0.001	P=0.753	P=0.003
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (includes multiple)[i]			
Overall rate	29/50 (58%)	39/50 (78%)	49/50 (98%)
Adjusted rate	59.8%	82.4%	99.3%
Terminal rate	22/41 (54%)	30/37 (81%)	36/36 (100%)
First incidence (days)	584	507	401
Poly-3 test	P<0.001	P=0.011	P<0.001

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
[a] Number of animals with lesion
[b] Historical incidence for 2-year NTP dermal studies with ethanol vehicle controls (mean ± standard deviation): 118/249 (47.4% ± 8.9%); range, 38%-62%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] 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 sacrifice.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	100 mg/kg	200 mg/kg
Female			
Number Examined Microscopically	50	50	50
Eosinophilic Focus	18	25	24
Hepatocellular Adenoma, Multiple	24	39	38
Hepatocellular Adenoma (includes multiple)[j]			
Overall rate	32/50 (64%)	44/50 (88%)	43/50 (86%)
Adjusted rate	69.0%	90.3%	90.7%
Terminal rate	26/35 (74%)	32/36 (89%)	25/26 (96%)
First incidence (days)	568	561	366
Poly-3 test	P=0.002	P=0.006	P=0.005
Hepatocellular Carcinoma, Multiple	2	4	16
Hepatocellular Carcinoma (includes multiple)[k]			
Overall rate	3/50 (6%)	21/50 (42%)	32/50 (64%)
Adjusted rate	6.6%	45.8%	70.4%
Terminal rate	1/35 (3%)	17/36 (47%)	18/26 (69%)
First incidence (days)	681	584	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma (includes multiple)			
Overall rate	33/50 (66%)	46/50 (92%)	48/50 (96%)
Adjusted rate	70.9%	94.4%	99.0%
Terminal rate	26/35 (74%)	34/36 (94%)	26/26 (100%)
First incidence (days)	568	561	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Hepatoblastoma, Multiple	0	0	1
Hepatoblastoma[l] (includes multiple)			
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.2%	7.3%
Terminal rate	0/35 (0%)	0/36 (0%)	1/26 (4%)
First incidence (days)	—[m]	629	567
Poly-3 test	P=0.054	P=0.498	P=0.103
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma (includes multiple)[n]			
Overall rate	33/50 (66%)	46/50 (92%)	48/50 (96%)
Adjusted rate	70.9%	94.4%	99.0%
Terminal rate	26/35 (74%)	34/36 (94%)	26/26 (100%)
First incidence (days)	568	561	366
Poly-3 test	P<0.001	P<0.001	P<0.001

[g] Historical incidence: 54/249 (21.7% ± 2.5%); range, 18%-24%
[h] Historical incidence: 1/249 (0.4% ± 0.9%); range, 0%-2%
[i] Historical incidence: 154/249 (61.8% ± 9.1%); range, 56%-78%
[j] Historical incidence: 133/252 (52.8% ± 11.4%); range, 38%-64%
[k] Historical incidence: 35/252 (13.9% ± 7.3%); range, 6%-23%
[l] Historical incidence: 1/252 (0.4% ± 0.9%); range, 0%-2%
[m] Not applicable; no neoplasms in animal group
[n] Historical incidence: 149/252 (59.1% ± 6.4%); range, 52%-66%

Kidney: The incidences of renal tubule adenoma (1/50, 1/50, 7/50) and of renal tubule adenoma or carcinoma (combined) (1/50, 1/50, 9/50) in 200 mg/kg males were significantly greater than those in the vehicle controls (Table C3) and exceeded the historical control ranges for these neoplasms [adenoma: 2/299 (0.7% ± 1.0%), range 0%-2%; adenoma or carcinoma 4/299 (1.3% ± 2.4%), range 0%-6%; Table C4b]. One 200 mg/kg female also had a renal tubule adenoma (Table D1). To further evaluate the response in female mice, an extended kidney analysis was conducted but no additional renal tubule neoplasms were found. The incidence of nephropathy in 200 mg/kg females was significantly less than that in the vehicle controls (27/50, 24/50, 15/50; Table D5).

Renal tubule hyperplasia, adenoma, and carcinoma formed a morphological continuum. Adenomas were focal, compressive masses approximately five or more tubules in diameter; carcinomas were morphologically similar to adenomas but were larger and often showed cellular debris and/or mineralization. Renal tubule neoplasms were located in the cortex or outer medulla. Focal proliferative masses less than five tubules in diameter were classified as focal hyperplasia.

Skin: No neoplasms of the skin were attributed to treatment with coconut oil acid diethanolamine condensate. Several nonneoplastic lesions of the skin at the site of application were determined to be chemical related. Incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in all dosed groups of males and females were significantly greater than those in the vehicle control groups (Tables 15, C5, and D5). The incidences of ulceration in 200 mg/kg males and

TABLE 15
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control		100 mg/kg		200 mg/kg	
Male						
Number Examined	50		50		50	
Microscopically						
Epidermis Hyperplasia[a]	5	(2.0)[b]	47**	(2.2)	50**	(2.9)
Sebaceous Gland, Hyperplasia	0		44**	(1.9)	49**	(2.0)
Inflammation	2	(3.5)	2	(1.0)	2	(2.5)
Parakeratosis	1	(2.0)	4	(1.0)	5	(1.0)
Hyperkeratosis	0		24**	(1.2)	23**	(1.4)
Ulcer	1	(4.0)	0		7*	(2.3)
Female						
Number Examined	50		50		50	
Microscopically						
Epidermis Hyperplasia	9	(2.1)	47**	(2.4)	50**	(3.0)
Sebaceous Gland, Hyperplasia	0		42**	(2.0)	48**	(1.9)
Inflammation	3	(1.3)	2	(1.0)	11*	(1.5)
Parakeratosis	3	(2.7)	4	(1.0)	16**	(1.3)
Hyperkeratosis	5	(1.4)	30**	(1.2)	40**	(1.9)
Ulcer	1	(1.0)	0		3	(1.3)

* 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

inflammation and parakeratosis in 200 mg/kg females were increased. Epidermal hyperplasia consisted of increased thickness of the epidermis and varied in severity from mild to moderate. Hyperkeratosis was usually of minimal to mild severity and consisted of increased keratin on the surface. In some cases, cells that had not shed their nuclei were undergoing keratinization, which is the basis for a diagnosis of parakeratosis. Parakeratosis was seen only with hyperkeratosis and was not considered to be biologically significant.

Thyroid Gland: The incidences of follicular cell hyperplasia in all dosed groups of males (vehicle control, 11/50; 100 mg/kg, 20/50; 200 mg/kg, 23/50; Table C5) and females (27/50, 36/50, 33/50; Table D5) were significantly greater than those in the vehicle controls. Follicular cell hyperplasia consisted of focal areas of thyroid gland follicles lined with increased numbers of epithelial cells, which formed papillary projections in some instances. The incidences of follicular cell adenoma (2/50, 5/50, 3/50; Table D3) in female mice administered 100 or 200 mg/kg were slightly, but not significantly, greater than that in the vehicle controls. While the incidence of follicular cell adenoma in 100 mg/kg females exceeded the historical control range [17/302 (5.6% ± 2.0%; range; 4%–8%), there was no dose-related pattern in the incidence of these neoplasms.

GENETIC TOXICOLOGY

Results of *in vitro* assays for genotoxicity with coconut oil acid diethanolamine condensate were uniformly negative. It did not induce mutations in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation (Zeiger *et al.*, 1988; Table E1). The highest concentration was limited to 200 μg/plate by toxicity. No increase in mutant L5178Y mouse lymphoma cell colonies was observed after exposure to coconut oil acid diethanolamine condensate, with or without S9 (Table E2). A single positive response noted at 8 nL/mL in the second trial conducted without S9 was not reproducible and the test results overall were considered to be negative. In tests for induction of chromosomal damage, no increases in the frequencies of sister chromatid exchanges (Table E3) or chromosomal aberrations (Table E4) were observed in cultured Chinese hamster ovary cells after incubation with coconut oil acid diethanolamine condensate, with or without S9.

In contrast to the negative results obtained in *in vitro* assays, positive results were obtained in the 14-week study. At the end of 14 weeks, significant increases in the frequencies of micronucleated normochromatic erythrocytes were seen in peripheral blood of both male and female mice (Table E5). Statistical analysis of the data showed positive trends for both data sets as well as significantly elevated micronucleus frequencies at the highest dose tested (800 mg/kg) in male and female mice.

DISCUSSION AND CONCLUSIONS

Coconut oil diethanolamide 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 by contact with the skin. Therefore, this series of studies was conducted by dermal administration.

During the 14-week studies in rats, doses of 200 or 400 mg coconut oil acid diethanolamine condensate/kg body weight were associated with reduced mean body weights and the presence of a minimal microcytic, normochromic, unresponsive anemia. The absence of a reticulocyte response or of any indication of hemosiderin in the spleen suggests that accelerated removal of erythrocytes was not involved. A similar anemia was observed in rats in the 14-week studies of diethanolamine. Because the coconut oil acid diethanolamine condensate preparation used in these studies contained approximately 18.2% free diethanolamine by weight, the anemia observed in this study may be associated with the contaminating diethanolamine. There was also an indication of altered lipid metabolism in the present study, as evidenced by decreases in cholesterol and triglyceride concentrations in the 200 and 400 mg/kg groups. Cholesterol and triglycerides were not measured in the diethanolamine study; however, diethanolamine is extensively incorporated into phospholipids (Matthews *et al.*, 1995), and *in vitro*, the choline analogs monomethyl and dimethylethanolamine inhibited incorporation of oleic acid into cholesteryl esters and triacylglycerols by 40% (Maziere *et al.*, 1990). Therefore, the unreacted diethanolamine may also be responsible for the changes in the cholesterol and triglyceride levels.

No neoplasms of the skin were associated with exposure to coconut oil acid diethanolamine condensate. At the end of the 2-year studies, the incidences of skin lesions at the site of application were significantly increased in all dosed groups of rats, but there were only slight differences in severities between the 50 and 100 mg/kg males or among any groups of females. In mice, the skin response was also rather mild; in males, the incidences of chronic inflammation were not increased at the site of application in groups exposed to coconut oil acid diethanolamine condensate, and in females, the incidences of ulcer were not increased in the dosed groups. In male and female mice, the severities of skin lesions were not increased by exposure to coconut oil acid diethanolamine condensate.

Renal tubule neoplasms were present in dosed groups of male and female rats. Six 50 mg/kg male rats had adenomas and one had a carcinoma; however, three vehicle control and three 100 mg/kg males had adenomas, and the incidences of hyperplasia were not increased. In female rats, there was a significant dose-related increase in the incidence of hyperplasia, and renal tubule carcinomas were present in two animals from the 50 mg/kg group, but there were no renal tubule neoplasms in the 100 mg/kg group.

In order to evaluate this response in greater detail, the kidneys from rats were step sectioned, and an extended evaluation of all kidney sections conducted. The extended evaluation identified additional renal tubule hyperplasias, adenomas, and a carcinoma in males and additional renal tubule hyperplasias and neoplasms in females. The number of renal tubule neoplasms in male rats identified by the extended evaluation was unusually large, but analysis of single and step sections combined indicates that the incidence

of renal tubule neoplasms in male rats was not increased by dermal exposure to coconut oil acid diethanolamine condensate, nor was there an increase in the incidence of renal tubule hyperplasia.

In female rats, the combined single and step section evaluations of the kidney revealed a significant dose-related increase in the incidence of renal tubule hyperplasia and two adenomas and two carcinomas in the 50 mg/kg group but only one neoplasm, an adenoma, in the 100 mg/kg group. Renal tubule neoplasms are uncommon in female F344/N rats, and the presence of four neoplasms in the 50 mg/kg group, combined with the increased incidence of hyperplasia, is suggestive of an association with chemical exposure. However, the absence of an increase in neoplasms the 100 mg/kg group in the presence of increased hyperplasia makes the association with chemical exposure uncertain.

The incidences of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were significantly increased in dosed male and female mice. The incidences of hepatoblastoma alone were significantly increased in male mice but not in female mice. Hepatoblastomas are uncommon phenotypic variants of hepatocellular carcinomas that appear to arise within existing hepatocellular carcinomas.

In addition, the incidences of renal tubule neoplasms were significantly increased in the 200 mg/kg group of male mice. A renal tubule adenoma was also present in one 200 mg/kg female mouse; however, an extended analysis of kidney sections failed to identify additional renal tubule neoplasms in any groups of female mice.

This pattern of response involving the liver of female mice and the liver and kidney of male mice is the same as that observed in mice in the 2-year studies of diethanolamine (NTP, 1999a) and fits into a pattern of response observed in the 2-year studies of 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 responses 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, 1998a). 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 hepatoblastoma 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.

The next strongest response was observed in the present study and involved significant increases in hepatocellular neoplasms in mice but no corresponding increases 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. Mean body weights and survival of 200 mg/kg female mice were less than those of vehicle controls. In addition, the incidences of renal tubule neoplasms were increased in 200 mg/kg male mice. The coconut oil acid diethanolamine condensate used for the present studies contained 18.2% free diethanolamine by weight. Therefore, mice in this study were exposed to 18.2 or 36.4 mg free diethanolamine/kg body weight.

The weakest positive response occurred in the lauric acid diethanolamine condensate study (NTP, 1999b), in which the incidences of hepatocellular neoplasms were increased only in female mice. Moreover, although the combined incidences of hepatocellular adenoma or carcinoma in dosed female mice were significantly greater than that in the vehicle controls, the incidences of hepatocellular adenoma or hepatocellular carcinoma alone were not significantly increased in 200 mg/kg female mice. Also, survival of females was similar to that of the vehicle controls, and no response was observed in the kidney of dosed male mice. Lauric acid diethanolamine condensate contained 0.83% free diethanolamine by weight, and,

therefore, mice in that study were exposed to 0.83 or 1.66 mg free diethanolamine/kg body weight.

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

To quantify the association between the incidence of hepatocellular neoplasms and diethanolamine concentration, a logistic regression model was fitted to individual animal neoplasm incidences and survival data from the four studies. The model predicts the incidence of hepatocellular neoplasms as a function of diethanolamine dose (mg/kg) and survival (days). This analysis compares observed liver neoplasm rates in female mice with the rates predicted by the logistic regression model (Figure 5). The close agreement between observed and predicted rates strongly supports the conclusion that the liver neoplasm response in the diethanolamine study and the three diethanolamine condensate studies is determined primarily by the concentration of free diethanolamine.

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 condensate, 0.83% free diethanolamine, and 9.17% other organic impurities. Oleic acid diethanolamine condensate was 47.5% oleic acid diethanolamine condensate, 0.19% free diethanolamine, approximately 30% other fatty acid alkanolamides, and 23.31% other organic impurities (most probably unreacted fatty acids). Coconut oil itself is a fatty acids mixture, which typically contains as much as 40% lauric acid, and this 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 for 100% diethanolamine.

Absorption, distribution, and metabolism studies of lauric acid diethanolamine condensate revealed that this diethanolamide is well absorbed after dermal exposure or oral administration and eliminated primarily in the urine as the half amides of succinic and adipic acid (Matthews *et al.*, 1996). No parent diethanolamide, diethanolamine, or diethanolamine-derived metabolites were detected in urine even after oral doses of 1,000 mg/kg. This suggests that lauric acid diethanolamine condensate metabolism involves ω-hydroxylation followed by β-oxidation to half amides that are eliminated in urine. Therefore, no additional bioavailable diethanolamine was released as a result of metabolic cleavage of the amide linkage, specifically for lauric acid diethanolamine condensate and quite likely for coconut oil diethanolamine condensate and oleic acid diethanolamine condensate. The results of the diethanolamine study and the other diethanolamine condensate studies are consistent with an association between the increased incidences of hepatocellular neoplasms in male and female mice, the increased incidences of renal tubule neoplasms in male mice, and the presence of free, unreacted diethanolamine.

The incidences of thyroid gland follicular cell hyperplasia were increased in male and female mice in the coconut oil acid diethanolamine condensate study. Similar increases in the incidences of thyroid gland follicular cell hyperplasia occurred in male and female mice in the diethanolamine study and in male mice in the lauric acid diethanolamine condensate study; no increase in the incidences of follicular cell hyperplasia occurred in male or female mice in the

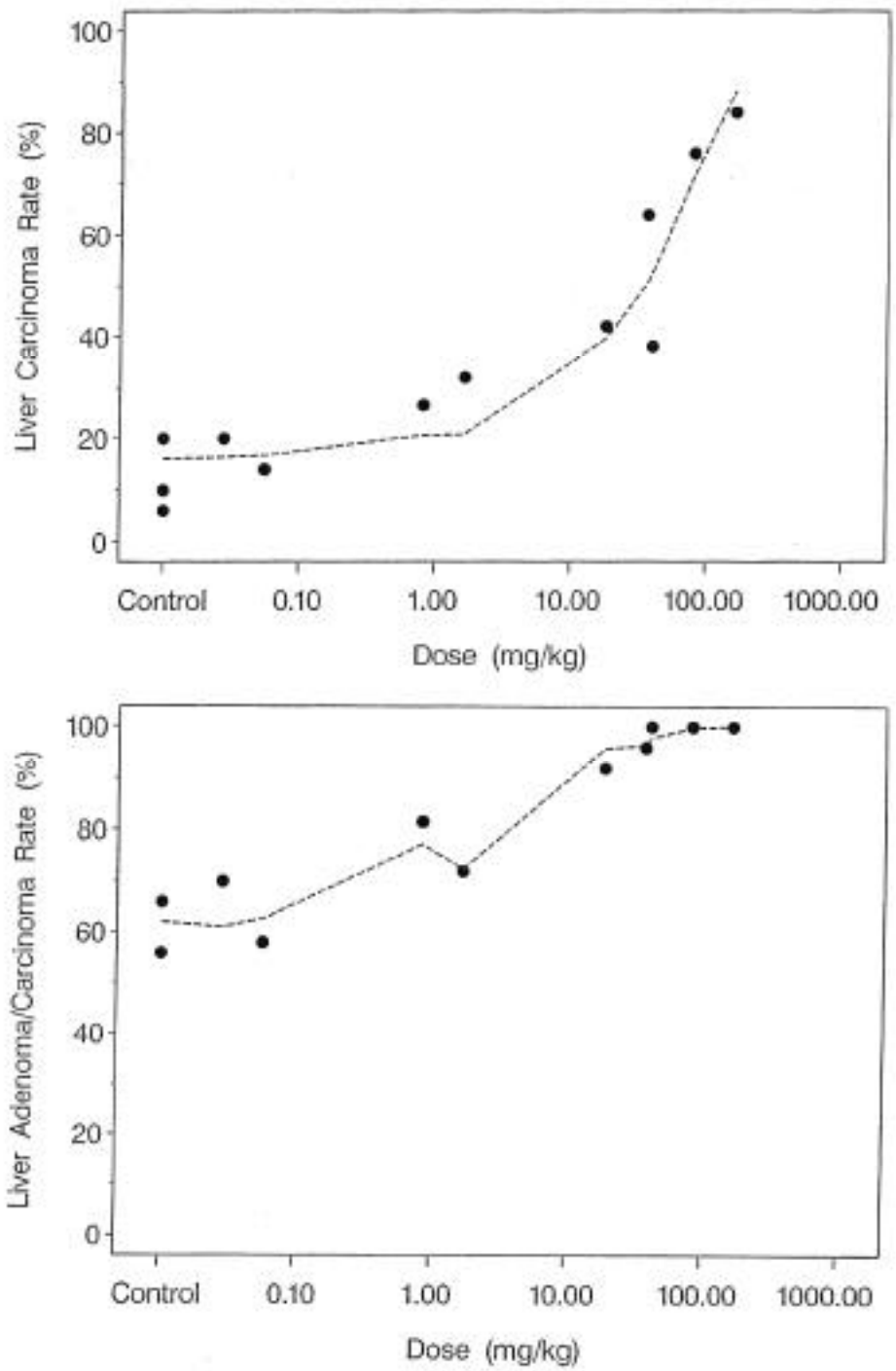


Figure 5
Observed and Predicted Liver Neoplasm Incidences in Female B6C3F$_1$ Mice as a Function of Dose and Survival (● = Observed, ---- = Predicted). Predicted rates are based on the logistic regression model, P=1/[1+exp(T)], where P is the probability of observing a neoplasm. For carcinoma, T = 3.2425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

oleic acid diethanolamine condensate study. Therefore, increased incidences of follicular cell hyperplasia also appear to be associated with dermal exposure to diethanolamine.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of coconut oil acid diethanolamine condensate in male F344/N rats administered 50 or 100 mg/kg. There was *equivocal evidence of carcinogenic activity* in female F344/N rats based on a marginal increase in the incidences of renal tubule neoplasms. There was *clear evidence of carcinogenic activity* in male $B6C3F_1$ mice based on increased incidences of hepatic and renal tubule neoplasms and in female $B6C3F_1$ mice based on increased incidences of hepatic neoplasms. These increases were associated with the concentration of free diethanolamine present as a contaminant in the diethanolamine condensate.

Exposure of rats to coconut oil acid diethanolamine condensate by dermal application in ethanol for 2 years resulted in epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, and parakeratosis in males and females and ulcer in females at the site of application. There were increases in the incidences of chronic inflammation, epithelial hyperplasia, and epithelial ulcer in the forestomach of female rats. The severities of nephropathy in dosed female rats were increased.

Exposure of mice to coconut oil acid diethanolamine condensate by dermal application for 2 years resulted in increased incidences of eosinophilic foci of the liver in males. Increased incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in males and females, ulcer in males, and parakeratosis and inflammation in females at the site of application and of follicular cell hyperplasia in the thyroid gland of males and females were chemical related.

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

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

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Coconut Oil 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	28	27	25
Natural deaths	13	11	14
Survivors			
Terminal sacrifice	8	12	11
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Thymoma malignant, metastatic, thymus			1 (2%)
Intestine large, colon	(50)	(50)	(50)
Polyp adenomatous		1 (2%)	1 (2%)
Intestine small, ileum	(50)	(50)	(50)
Liver	(50)	(50)	(50)
Mesentery	(8)	(7)	(6)
Fat, fibrosarcoma		1 (14%)	
Oral mucosa	(1)	(2)	(2)
Gingival, squamous cell carcinoma			1 (50%)
Pharyngeal, squamous cell papilloma	1 (100%)		
Pancreas	(50)	(50)	(50)
Acinus, adenoma	1 (2%)		
Salivary glands	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)		1 (2%)
Squamous cell papilloma, multiple		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma		1 (2%)	
Adrenal medulla	(50)	(50)	(50)
Ganglioneuroma		1 (2%)	
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma benign	6 (12%)	4 (8%)	5 (10%)
Bilateral, pheochromocytoma benign		1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	3 (6%)	4 (8%)	3 (6%)
Pituitary gland	(50)	(50)	(49)
Sarcoma, metastatic, brain	1 (2%)		
Pars distalis, adenoma	37 (74%)	39 (78%)	36 (73%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	4 (8%)	4 (8%)
C-cell, carcinoma			1 (2%)
Follicular cell, adenoma		3 (6%)	1 (2%)
Follicular cell, carcinoma	2 (4%)		1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	
General Body System				
Peritoneum		(1)		
Genital System				
Epididymis	(50)	(50)	(50)	
Preputial gland	(50)	(50)	(50)	
Adenoma		2 (4%)	1 (2%)	
Carcinoma		1 (2%)	2 (4%)	
Bilateral, adenoma	1 (2%)			
Prostate		(50)	(50)	(50)
Carcinoma	2 (4%)			
Seminal vesicle	(50)	(50)	(50)	
Testes	(50)	(50)	(50)	
Bilateral, interstitial cell, adenoma	11 (22%)	9 (18%)	12 (24%)	
Interstitial cell, adenoma	12 (24%)	11 (22%)	7 (14%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	
Lymph node	(35)	(30)	(37)	
Mediastinal, fibrosarcoma, metastatic, skin		1 (3%)		
Lymph node, mandibular	(50)	(50)	(50)	
Lymph node, mesenteric	(49)	(50)	(50)	
Spleen	(50)	(50)	(50)	
Hemangiosarcoma		1 (2%)		
Thymus		(47)	(45)	(48)
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(48)	(49)	(50)	
Adenoma	1 (2%)			
Carcinoma		1 (2%)	1 (2%)	
Fibroadenoma	2 (4%)	1 (2%)	1 (2%)	
Skin	(50)	(50)	(50)	
Basal cell carcinoma	1 (2%)			
Keratoacanthoma	2 (4%)	4 (8%)		
Squamous cell papilloma	1 (2%)	1 (2%)		
Trichoepithelioma			1 (2%)	
Pinna, squamous cell papilloma		1 (2%)		
Sebaceous gland, carcinoma		1 (2%)		
Sebaceous gland, skin, site of application, adenoma	1 (2%)			
Skin, site of application, basal cell adenoma		1 (2%)		
Skin, site of application, basal cell carcinoma	1 (2%)			
Skin, site of application, keratoacanthoma	1 (2%)	2 (4%)		
Subcutaneous tissue, fibroma	3 (6%)	3 (6%)	1 (2%)	
Subcutaneous tissue, fibrosarcoma		2 (4%)	1 (2%)	
Subcutaneous tissue, skin, site of application, fibrosarcoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	
Osteosarcoma		1 (2%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg
Nervous System			
Brain	(50)	(50)	(50)
Cranial nerve, schwannoma malignant	1 (2%)		
Meninges, sarcoma	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Thymoma malignant, metastatic, thymus			1 (2%)
Nose	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Special Senses System			
Zymbal's gland	(1)	(2)	
Carcinoma	1 (100%)	2 (100%)	
Urinary System			
Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
Thymoma malignant, metastatic, thymus			1 (2%)
Renal tubule, adenoma	3 (6%)	4 (8%)	3 (6%)
Renal tubule, adenoma, multiple		2 (4%)	
Renal tubule, carcinoma		1 (2%)	
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia granulocytic		1 (2%)	
Leukemia mononuclear	16 (32%)	10 (20%)	12 (24%)
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	49	49	49
Total primary neoplasms	119	125	101
Total animals with benign neoplasms	48	49	47
Total benign neoplasms	92	101	78
Total animals with malignant neoplasms	25	20	21
Total malignant neoplasms	27	24	23
Total animals with metastatic neoplasms	1	1	1
Total metastatic neoplasms	1	1	3

[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 Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	110	334	389	392	442	458	463	467	470	495	521	526	540	543	556	561	563	583	583	589	591	593	603	607	617
Carcass ID Number	027	031	033	016	004	024	013	026	038	036	001	049	043	025	029	042	014	023	048	028	006	020	022	046	018
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+						+				+										+		
Oral mucosa																		+							
Pharyngeal, squamous cell papilloma																		X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Parathyroid gland	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, brain								X																	
Pars distalis, adenoma		X	X	X	X	X	X	X	X			X	X	X	X	X	X			X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X													
Follicular cell, carcinoma											X														
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																			+						
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X								X	X					
Interstitial cell, adenoma								X									X					X		X	

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

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

Number of Days on Study	618	618	621	631	632	640	642	650	656	668	677	680	702	705	713	713	723	729	729	729	729	729	729	729	729	
Carcass ID Number	007	032	019	002	005	011	034	010	003	047	008	039	050	040	012	030	037	009	015	017	021	035	041	044	045	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+				+							+				+		8
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X											X		3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X	X	X					X													X					6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X								X												3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, brain																										1
Pars distalis, adenoma	X	X		X		X	X	X	X	X	X	X	X			X				X	X		X	X	X	37
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X			X			3
Follicular cell, carcinoma		X																								2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, adenoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X		X												2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X				X						X				X	X	X	X				X				11
Interstitial cell, adenoma				X		X				X			X	X					X				X		X	12

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

Number of Days on Study	1	3	3	3	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6
	1	3	8	9	4	5	6	6	7	9	2	2	4	4	5	6	6	8	8	8	9	9	0	0	1
	0	4	9	2	2	8	3	7	0	5	1	6	0	3	6	1	3	3	3	9	1	3	3	7	7
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	3	3	1	0	2	1	2	3	3	0	4	4	2	2	4	1	2	4	2	0	2	2	4	1
	7	1	3	6	4	4	3	6	8	6	1	9	3	5	9	2	4	3	8	8	6	0	2	6	8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+			+	+	+	+	+	+	+	+	+	+	+		+			+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma								X																	
Squamous cell papilloma																									
Sebaceous gland, skin, site of application, adenoma																							X		
Skin, site of application, basal cell carcinoma				X																					
Skin, site of application, keratoacanthoma																									
Subcutaneous tissue, fibroma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranial nerve, schwannoma malignant						X																			
Meninges, sarcoma								X																	
Peripheral nerve																+									
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									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 Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	618	618	621	631	632	640	442	650	656	668	667	680	702	705	713	713	723	729	729	729	729	729	729	729	729	
Carcass ID Number	007	032	019	002	005	011	034	010	003	047	008	039	050	040	012	030	037	009	015	017	021	035	041	044	045	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+		+	+	+	+	+	+	+	+				+	+	+	+	+	+			+	35
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Fibroadenoma																							X		X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																					X					1
Keratoacanthoma				X																						2
Squamous cell papilloma																		X								1
Sebaceous gland, skin, site of application, adenoma 1																										
Skin, site of application, basal cell carcinoma																										1
Skin, site of application, keratoacanthoma															X											1
Subcutaneous tissue, fibroma			X																			X				3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranial nerve, schwannoma malignant																										1
Meninges, sarcoma																										1
Peripheral nerve						+											+									3
Spinal cord						+											+									3
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+									+							2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma							X						X													3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X	X	X	X	X		X					X		X	X		X				16
Mesothelioma malignant																							X			2

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

Number of Days on Study	380	444	474	495	499	511	523	529	534	558	561	574	575	579	580	586	589	600	611	611	617	617	620	620	621
Carcass ID Number	083	075	059	084	072	076	058	077	071	064	094	079	095	056	073	054	052	087	062	098	053	060	065	069	088
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+									+											
Fat, fibrosarcoma																									
Oral mucosa																				+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma							X																		
Pheochromocytoma malignant																									
Pheochromocytoma benign																X									
Bilateral, pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
Follicular cell, adenoma																									
General Body System																									
Peritoneum																									
Genital System																									
Coagulating gland																	+								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																							X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma					X			X				X		X		X							X		

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

Number of Days on Study	626	656	656	670	677	686	695	708	710	713	720	725	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	057	086	089	085	093	081	090	096	099	092	051	070	097	095	061	063	066	067	068	074	078	080	082	091	010	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous											X															1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery								+				+								+			+	+		7
Fat, fibrosarcoma																				X						1
Oral mucosa							+																			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma, multiple															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Pheochromocytoma malignant													X													1
Pheochromocytoma benign		X									X				X											4
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X						X		X										4
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	46
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			39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X	X																X							4
Follicular cell, adenoma																	X				X				X	3
General Body System																										
Peritoneum																							+			1
Genital System																										
Coagulating gland												+						+								3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma							X	X						X		X		X	X	X				X	X	9
Interstitial cell, adenoma			X	X					X	X													X			11

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

Number of Days on Study	380	444	474	495	499	511	523	529	534	558	561	574	575	579	580	586	589	600	611	611	617	617	620	620	621
Carcass ID Number	083	075	059	084	072	076	058	077	071	064	094	079	095	056	073	054	052	087	062	098	053	060	065	069	088
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+	+		+		+				+	+		+	+	+		+			+	+	+
Mediastinal, fibrosarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X							
Squamous cell papilloma																							X		
Pinna, squamous cell papilloma																									
Sebaceous gland, carcinoma																		X							
Skin, site of application, basal cell adenoma																									
Skin, site of application, keratoacanthoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland								+											+						
Carcinoma								X											X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Renal tubule, adenoma																								X	
Renal tubule, adenoma, multiple																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic														X											
Leukemia mononuclear								X						X			X						X		X
Mesothelioma malignant																									

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

Number of Days on Study	626	656	656	670	677	686	695	708	710	713	720	725	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	057	086	089	085	093	081	090	096	099	092	051	070	097	095	061	063	066	067	068	074	078	080	082	091	010	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+		+		+			+	+		+	+		+	+		+		+	+			30
Mediastinal, fibrosarcoma, metastatic, skin												X														1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma										X																1
Fibroadenoma				X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma						X									X	X										4
Squamous cell papilloma																										1
Pinna, squamous cell papilloma														X												1
Sebaceous gland, carcinoma																										1
Skin, site of application, basal cell adenoma							X																			1
Skin, site of application, keratoacanthoma										X											X					2
Subcutaneous tissue, fibroma	X										X								X							3
Subcutaneous tissue, fibrosarcoma												X				X										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+						+										+						3
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																		X								1
Renal tubule, adenoma							X			X			X													4
Renal tubule, adenoma, multiple																		X						X		2
Renal tubule, carcinoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Leukemia mononuclear		X									X				X		X	X								10
Mesothelioma malignant																							X			1

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

Number of Days on Study	329	389	421	474	485	505	508	529	552	560	560	562	565	579	582	586	593	607	607	620	621	626	627	632	640
Carcass ID Number	128	147	146	131	134	106	112	123	118	107	129	117	103	108	119	114	143	109	124	137	127	135	115	130	145
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus		X																							
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+														+	+								+
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X				X		
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	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
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X											
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Carcinoma									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X			X						X					X		
Interstitial cell, adenoma															X										

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

Number of Days on Study	656	666	674	677	687	688	690	695	698	698	701	702	711	719	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	144	138	148	132	101	104	126	140	121	141	113	142	110	139	102	105	111	116	120	122	125	133	136	149	150	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma malignant, metastatic, thymus																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous		X																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+		+										6
Oral mucosa		+		+																						2
Gingival, squamous cell carcinoma		X																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X	X							X		5
Bilateral, pheochromocytoma benign																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X			X					X		3
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X	X			X	X	X	X	X	X	X			X	X	X	X	X				36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X									X								X			4
C-cell, carcinoma																		X								1
Follicular cell, adenoma																						X				1
Follicular cell, carcinoma											X															1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma				X																						2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X					X						X			X			X	X			X		X	12
Interstitial cell, adenoma								X	X						X		X				X			X		7

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

Number of Days on Study	329	389	421	474	485	505	508	529	552	560	560	562	565	579	582	586	593	607	607	620	621	626	627	632	640
Carcass ID Number	128	147	146	131	134	106	112	123	118	107	129	117	103	108	119	114	143	109	124	137	127	135	115	130	145
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+		+	+		+		+		+	+	+	+	+	+	+		+	+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																							X		
Subcutaneous tissue, fibroma					X																				
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, skin, site of application, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+			+										+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus		X																							
Renal tubule, adenoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X											X					X			X		X
Mesothelioma malignant							X																		

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

Number of Days on Study	656	666	674	677	687	688	690	695	698	698	701	702	711	719	729	729	729	729	729	729	729	729	729	729	729		
Carcass ID Number	144	138	148	132	101	104	126	140	121	141	113	142	110	139	102	105	111	116	120	122	125	133	136	149	150		Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+		+		+	+	+	+		+	+	+	+	+	+	+		+	+		+	+		+	+		37
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymoma malignant																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma																	X										1
Fibroadenoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trichoepithelioma																											1
Subcutaneous tissue, fibroma																											1
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, skin, site of application, fibrosarcoma		X																									1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymoma malignant, metastatic, thymus																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Eye											+		+						+		+		+				8
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymoma malignant, metastatic, thymus																											1
Renal tubule, adenoma	X																		X								3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear		X			X							X		X	X	X			X								12
Mesothelioma malignant																											1

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	6/50 (12%)	5/50 (10%)	6/50 (12%)
Adjusted rate[b]	18.7%	14.0%	17.1%
Terminal rate[c]	1/8 (13%)	1/12 (8%)	4/11 (36%)
First incidence (days)	603	586	607
Poly-3 test[d]	P=0.511N	P=0.422N	P=0.561N
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted rate	18.7%	16.8%	17.1%
Terminal rate	1/8 (13%)	1/12 (8%)	4/11 (36%)
First incidence (days)	603	586	607
Poly-3 test	P=0.503N	P=0.545N	P=0.561N
Kidney (Renal Tubule): Adenoma (Single Sections)			
Overall rate	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted rate	9.6%	17.1%	8.6%
Terminal rate	0/8 (0%)	2/12 (17%)	1/11 (9%)
First incidence (days)	593	620	565
Poly-3 test	P=0.491N	P=0.300	P=0.608N
Kidney (Renal Tubule): Adenoma (Step Sections)			
Overall rate	8/50 (16%)	8/50 (16%)	8/50 (16%)
Adjusted rate	24.6%	22.4%	22.2%
Terminal rate	1/8 (13%)	3/12 (25%)	3/11 (27%)
First incidence (days)	442	575	389
Poly-3 test	P=0.472N	P=0.530N	P=0.524N
Kidney (Renal Tubule): Adenoma (Single and Step Sections)			
Overall rate	11/50 (22%)	10/50 (20%)	10/50 (20%)
Adjusted rate	32.9%	28.0%	27.4%
Terminal rate	1/8 (13%)	4/12 (33%)	4/11 (36%)
First incidence (days)	442	575	389
Poly-3 test	P=0.358N	P=0.425N	P=0.403N
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)			
Overall rate	3/50 (6%)	7/50 (14%)	3/50 (6%)
Adjusted rate	9.6%	19.8%	8.6%
Terminal rate	0/8 (0%)	2/12 (17%)	1/11 (9%)
First incidence (days)	593	620	565
Poly-3 test	P=0.480N	P=0.207	P=0.608N
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections)			
Overall rate	8/50 (16%)	9/50 (18%)	8/50 (16%)
Adjusted rate	24.6%	25.2%	22.2%
Terminal rate	1/8 (13%)	3/12 (25%)	3/11 (27%)
First incidence (days)	442	575	389
Poly-3 test	P=0.465N	P=0.590	P=0.524N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)			
Overall rate	11/50 (22%)	11/50 (22%)	10/50 (20%)
Adjusted rate	32.9%	30.5%	27.4%
Terminal rate	1/8 (13%)	4/12 (33%)	4/11 (36%)
First incidence (days)	442	575	389
Poly-3 test	P=0.354N	P=0.520N	P=0.403N
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	9.8%	2.9%	2.9%
Terminal rate	2/8 (25%)	0/12 (0%)	0/11 (0%)
First incidence (days)	563	670	621
Poly-3 test	P=0.182N	P=0.260N	P=0.261N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.8%	5.7%	5.8%
Terminal rate	2/8 (25%)	0/12 (0%)	1/11 (9%)
First incidence (days)	563	670	621
Poly-3 test	P=0.367N	P=0.442N	P=0.445N
Pancreatic Islets: Adenoma			
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	9.7%	11.3%	8.8%
Terminal rate	0/8 (0%)	2/12 (17%)	3/11 (27%)
First incidence (days)	607	523	729 (T)
Poly-3 test	P=0.530N	P=0.571	P=0.619N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	37/50 (74%)	39/50 (78%)	36/49 (73%)
Adjusted rate	80.8%	83.5%	77.6%
Terminal rate	5/8 (63%)	8/12 (67%)	6/11 (55%)
First incidence (days)	334	444	329
Poly-3 test	P=0.392N	P=0.472	P=0.451N
Preputial Gland: Adenoma or Carcinoma			
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted rate	3.3%	8.5%	8.5%
Terminal rate	1/8 (13%)	1/12 (8%)	0/11 (0%)
First incidence (days)	729 (T)	611	552
Poly-3 test	P=0.307	P=0.362	P=0.362
Skin: Keratoacanthoma			
Overall rate	3/50 (6%)	6/50 (12%)	0/50 (0%)
Adjusted rate	9.6%	17.0%	0.0%
Terminal rate	0/8 (0%)	3/12 (25%)	0/11 (0%)
First incidence (days)	467	600	—[e]
Poly-3 test	P=0.105N	P=0.297	P=0.101N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Skin: Squamous Cell Papilloma or Keratoacanthoma			
Overall rate	4/50 (8%)	8/50 (16%)	0/50 (0%)
Adjusted rate	12.7%	22.4%	0.0%
Terminal rate	1/8 (13%)	4/12 (33%)	0/11 (0%)
First incidence (days)	467	600	—
Poly-3 test	P=0.059N	P=0.234	P=0.047N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma			
Overall rate	6/50 (12%)	9/50 (18%)	1/50 (2%)
Adjusted rate	18.6%	25.2%	2.9%
Terminal rate	2/8 (25%)	4/12 (33%)	0/11 (0%)
First incidence (days)	392	600	627
Poly-3 test	P=0.043N	P=0.358	P=0.041N
Skin (Subcutaneous Tissue): Fibroma			
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	9.7%	8.6%	2.9%
Terminal rate	1/8 (13%)	1/12 (8%)	0/11 (0%)
First incidence (days)	603	626	485
Poly-3 test	P=0.197N	P=0.608N	P=0.261N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rate	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted rate	9.7%	14.3%	8.4%
Terminal rate	1/8 (13%)	2/12 (17%)	0/11 (0%)
First incidence (days)	603	626	485
Poly-3 test	P=0.490N	P=0.422	P=0.597N
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	9.8%	2.9%	2.9%
Terminal rate	1/8 (13%)	1/12 (8%)	0/11 (0%)
First incidence (days)	617	729 (T)	552
Poly-3 test	P=0.181N	P=0.261N	P=0.259N
Testes: Adenoma			
Overall rate	23/50 (46%)	20/50 (40%)	19/50 (38%)
Adjusted rate	63.6%	51.8%	50.8%
Terminal rate	5/8 (63%)	8/12 (67%)	9/11 (82%)
First incidence (days)	467	499	552
Poly-3 test	P=0.147N	P=0.192N	P=0.169N
Thyroid Gland (C-cell): Adenoma			
Overall rate	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted rate	9.7%	11.3%	11.5%
Terminal rate	2/8 (25%)	1/12 (8%)	2/11 (18%)
First incidence (days)	526	621	579
Poly-3 test	P=0.498	P=0.578	P=0.569

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

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted rate	9.7%	11.3%	14.3%
Terminal rate	2/8 (25%)	1/12 (8%)	3/11 (27%)
First incidence (days)	526	621	579
Poly-3 test	P=0.353	P=0.578	P=0.424
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	8.7%	2.9%
Terminal rate	0/8 (0%)	3/12 (25%)	1/11 (9%)
First incidence (days)	—	729 (T)	729 (T)
Poly-3 test	P=0.452	P=0.142	P=0.525
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.4%	8.7%	5.8%
Terminal rate	0/8 (0%)	3/12 (25%)	1/11 (9%)
First incidence (days)	521	729 (T)	701
Poly-3 test	P=0.553N	P=0.547	P=0.661N
All Organs: Mononuclear Cell Leukemia			
Overall rate	16/50 (32%)	10/50 (20%)	12/50 (24%)
Adjusted rate	45.0%	26.8%	32.3%
Terminal rate	3/8 (38%)	3/12 (25%)	3/11 (27%)
First incidence (days)	470	529	474
Poly-3 test	P=0.155N	P=0.075N	P=0.181N
All Organs: Benign Neoplasms			
Overall rate	48/50 (96%)	49/50 (98%)	47/50 (94%)
Adjusted rate	99.3%	99.7%	97.5%
Terminal rate	8/8 (100%)	12/12 (100%)	11/11 (100%)
First incidence (days)	334	444	329
Poly-3 test	P=0.297N	P=0.991	P=0.543N
All Organs: Malignant Neoplasms			
Overall rate	25/50 (50%)	20/50 (40%)	21/50 (42%)
Adjusted rate	63.5%	51.6%	51.8%
Terminal rate	5/8 (63%)	6/12 (50%)	5/11 (46%)
First incidence (days)	392	529	389
Poly-3 test	P=0.158N	P=0.182N	P=0.186N

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

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Benign or Malignant Neoplasms			
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	100.0%	99.7%	98.4%
Terminal rate	8/8 (100%)	12/12 (100%)	11/11 (100%)
First incidence (days)	334	444	329
Poly-3 test	P=0.336N	P=1.000N	P=0.609N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary gland, 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
Historical Incidence of Renal Tubule Neoplasms in Vehicle Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Benzethonium Chloride	0/52	0/52	0/52
Coconut Oil Acid Diethanolamine Condensate	3/50	0/50	3/50
Diethanolamine	0/50	0/50	0/50
Lauric Acid Diethanolamine Condensate	0/50	0/50	0/50
Oleic Acid Diethanolamine Condensate	3/50	1/50	4/50
Sodium Xylenesulfonate	2/50	0/50	2/50
Overall Historical Incidence			
Total	8/302 (2.6%)	1/302 (0.3%0	9/302 (3.0%)
Mean ± standard deviation	2.7% ± 3.0%	0.3% ± 0.8%	3.0% ± 3.5%
Range	0%-6%	0%-2%	0%-8%

[a] Data as of 12 July 2000

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Coconut Oil 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	28	27	25
Natural deaths	13	11	14
Survivors			
Terminal sacrifice	8	12	11
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(50)	(50)	(50)
Parasite metazoan	2 (4%)	5 (10%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)
Parasite metazoan	2 (4%)	5 (10%)	
Intestine large, cecum	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)		
Parasite metazoan			1 (2%)
Ulcer	1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)
Epithelium, ulcer			1 (2%)
Liver	(50)	(50)	(50)
Basophilic focus	3 (6%)	13 (26%)	3 (6%)
Clear cell focus	3 (6%)	6 (12%)	2 (4%)
Eosinophilic focus		1 (2%)	
Fibrosis		1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	9 (18%)	8 (16%)
Inflammation, chronic	20 (40%)	25 (50%)	24 (48%)
Mineralization	1 (2%)		
Vacuolization cytoplasmic	27 (54%)	36 (72%)	33 (66%)
Bile duct, hyperplasia	47 (94%)	48 (96%)	50 (100%)
Hepatocyte, degeneration, cystic	8 (16%)	8 (16%)	3 (6%)
Hepatocyte, necrosis	1 (2%)	3 (6%)	1 (2%)
Hepatocyte, centrilobular, degeneration	2 (4%)	1 (2%)	
Hepatocyte, centrilobular, necrosis	2 (4%)	1 (2%)	
Portal vein, thrombosis			1 (2%)
Mesentery	(8)	(7)	(6)
Accessory spleen		1 (14%)	
Inflammation, chronic active	1 (13%)	1 (14%)	
Fat, necrosis	7 (88%)	3 (43%)	5 (83%)
Oral mucosa	(1)	(2)	(2)
Gingival, hyperplasia		1 (50%)	
Gingival, inflammation, chronic active		1 (50%)	1 (50%)
Pharyngeal, hyperplasia, squamous		1 (50%)	
Pancreas	(50)	(50)	(50)
Acinus, atrophy	11 (22%)	22 (44%)	25 (50%)
Artery, inflammation, chronic active	1 (2%)		
Salivary glands	(50)	(50)	(50)
Duct, cyst	1 (2%)		

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Stomach, forestomach	(50)	(50)	(50)
Edema	6 (12%)	5 (10%)	8 (16%)
Foreign body			1 (2%)
Inflammation, chronic active	15 (30%)	8 (16%)	14 (28%)
Mineralization	4 (8%)	2 (4%)	2 (4%)
Perforation	4 (8%)	2 (4%)	4 (8%)
Epithelium, hyperplasia	18 (36%)	16 (32%)	18 (36%)
Epithelium, ulcer	13 (26%)	7 (14%)	13 (26%)
Stomach, glandular	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		2 (4%)
Mineralization	7 (14%)	6 (12%)	4 (8%)
Epithelium, erosion			2 (4%)
Epithelium, ulcer			3 (6%)
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Mineralization	1 (2%)		
Aorta, mineralization	6 (12%)	4 (8%)	4 (8%)
Pulmonary artery, mineralization	4 (8%)		2 (4%)
Heart	(50)	(50)	(50)
Cardiomyopathy, chronic	37 (74%)	43 (86%)	42 (84%)
Inflammation, suppurative	1 (2%)		
Mineralization	5 (10%)	3 (6%)	4 (8%)
Atrium, thrombosis	6 (12%)	1 (2%)	1 (2%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule		2 (4%)	1 (2%)
Atypia cellular			1 (2%)
Degeneration, cystic	3 (6%)	4 (8%)	3 (6%)
Degeneration, fatty	36 (72%)	40 (80%)	38 (76%)
Hyperplasia	13 (26%)	21 (42%)	24 (48%)
Hypertrophy	2 (4%)	6 (12%)	5 (10%)
Necrosis	1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	20 (40%)	19 (38%)	16 (32%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	
Parathyroid gland	(48)	(46)	(45)
Hyperplasia	14 (29%)	15 (33%)	8 (18%)
Pituitary gland	(50)	(50)	(49)
Pigmentation, hematoidin		1 (2%)	
Pars distalis, cyst	16 (32%)	7 (14%)	3 (6%)
Pars distalis, hyperplasia	13 (26%)	10 (20%)	12 (24%)
Pars intermedia, cyst	1 (2%)		1 (2%)
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia	6 (12%)	11 (22%)	11 (22%)
Follicle, cyst	2 (4%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
General Body System			
None			
Genital System			
Coagulating gland		(3)	
Inflammation, chronic active		1 (33%)	
Inflammation, suppurative		2 (67%)	
Epididymis	(50)	(50)	(50)
Mineralization	1 (2%)		
Preputial gland	(50)	(50)	(50)
Hyperplasia	3 (6%)	1 (2%)	3 (6%)
Inflammation, chronic active	47 (94%)	46 (92%)	46 (92%)
Prostate	(50)	(50)	(50)
Cyst multilocular	9 (18%)	8 (16%)	4 (8%)
Inflammation, chronic active	46 (92%)	47 (94%)	46 (92%)
Seminal vesicle	(50)	(50)	(50)
Dilatation	1 (2%)		
Testes	(50)	(50)	(50)
Arteriole, inflammation, chronic	9 (18%)	11 (22%)	13 (26%)
Arteriole, necrosis, fibrinoid	9 (18%)	10 (20%)	13 (26%)
Bilateral, germinal epithelium, atrophy	1 (2%)		1 (2%)
Germinal epithelium, atrophy	10 (20%)	15 (30%)	16 (32%)
Interstitial cell, hyperplasia	12 (24%)	12 (24%)	13 (26%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Atrophy	1 (2%)		
Hyperplasia	22 (44%)	22 (44%)	16 (32%)
Lymph node	(35)	(30)	(37)
Mediastinal, hyperplasia, lymphoid		1 (3%)	
Mediastinal, pigmentation, hemosiderin	29 (83%)	26 (87%)	33 (89%)
Lymph node, mandibular	(50)	(50)	(50)
Ectasia			1 (2%)
Hyperplasia, plasma cell		1 (2%)	
Lymph node, mesenteric	(49)	(50)	(50)
Ectasia	1 (2%)	2 (4%)	
Infiltration cellular, histiocyte	1 (2%)		
Spleen	(50)	(50)	(50)
Fibrosis	6 (12%)	5 (10%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	3 (6%)
Hyperplasia		1 (2%)	
Hyperplasia, lymphoid			1 (2%)
Necrosis	1 (2%)		
Red pulp, depletion cellular	2 (4%)		1 (2%)
Thymus	(47)	(45)	(48)
Ectopic parathyroid gland			1 (2%)
Integumentary System			
Mammary gland	(48)	(49)	(50)
Cyst	2 (4%)	6 (12%)	4 (8%)
Hyperplasia, cystic	36 (75%)	44 (90%)	43 (86%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System (continued)			
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)		
Inflammation, chronic active		2 (4%)	
Epidermis, hyperkeratosis			1 (2%)
Epidermis, hyperplasia			1 (2%)
Epidermis, skin, site of application, hyperkeratosis		36 (72%)	48 (96%)
Epidermis, skin, site of application, hyperplasia		46 (92%)	50 (100%)
Epidermis, skin, site of application, parakeratosis		9 (18%)	28 (56%)
Epidermis, skin, site of application, ulcer		1 (2%)	1 (2%)
Prepuce, inflammation, chronic active	1 (2%)		
Sebaceous gland, skin, site of application, hyperplasia		45 (90%)	50 (100%)
Skin, site of application, hemorrhage		1 (2%)	
Skin, site of application, inflammation, chronic active		1 (2%)	2 (4%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Callus	1 (2%)		
Fibrous osteodystrophy	10 (20%)	12 (24%)	6 (12%)
Nervous System			
Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Mineralization			1 (2%)
Respiratory System			
Lung	(50)	(50)	(50)
Fibrosis	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, chronic active	2 (4%)	8 (16%)	2 (4%)
Inflammation, granulomatous	2 (4%)		
Inflammation, suppurative	1 (2%)		
Mineralization	2 (4%)		
Alveolar epithelium, hyperplasia	2 (4%)	4 (8%)	1 (2%)
Alveolus, infiltration cellular, histiocyte	7 (14%)	13 (26%)	12 (24%)
Interstitium, mineralization	2 (4%)	4 (8%)	2 (4%)
Nose	(50)	(50)	(50)
Inflammation, chronic active	9 (18%)	7 (14%)	10 (20%)
Inflammation, suppurative		1 (2%)	
Nasolacrimal duct, inflammation, suppurative	2 (4%)	4 (8%)	4 (8%)
Respiratory epithelium, hyperplasia	9 (18%)	7 (14%)	9 (18%)
Respiratory epithelium, metaplasia, squamous	3 (6%)	2 (4%)	3 (6%)
Vein, turbinate, septum, thrombosis	2 (4%)		2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate

	Vehicle Control	50 mg/kg	100 mg/kg
Special Senses System			
Eye	(2)	(3)	(8)
Cornea, inflammation, chronic active		1 (33%)	
Cornea, mineralization		1 (33%)	
Lens, cataract	2 (100%)	2 (67%)	8 (100%)
Retina, atrophy	2 (100%)	2 (67%)	8 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)	1 (2%)
Cyst	8 (16%)	9 (18%)	7 (14%)
Hydronephrosis	1 (2%)		
Mineralization	3 (6%)	3 (6%)	3 (6%)
Nephropathy, chronic	49 (98%)	50 (100%)	49 (98%)
Pigmentation, hemosiderin	43 (86%)	44 (88%)	50 (100%)
Renal tubule, hyperplasia	13 (26%)	13 (26%)	15 (30%)
Urinary bladder	(50)	(50)	(50)
Calculus, gross observation		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, chronic active	2 (4%)	1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)

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

TABLE B1 Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate 91

TABLE B2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate 94

TABLE B3 Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate 106

TABLE B4 Historical Incidence of Renal Tubule Neoplasms in Vehicle Control Female F344/N Rats 109

TABLE B5 Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate 110

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	7	15	10
Natural deaths	15	11	18
Survivors			
Died last week of study			1
Terminal sacrifice	28	24	21
Animals examined microscopically	50	50	50
Alimentary System			
Intestine small, duodenum	(50)	(50)	(50)
Liver	(50)	(50)	(50)
Hepatocellular adenoma			1 (2%)
Histiocytic sarcoma	1 (2%)		
Mesentery	(4)	(5)	(2)
Oral mucosa	(1)	(1)	(3)
Gingival, squamous cell carcinoma			1 (33%)
Pancreas	(50)	(50)	(50)
Salivary glands	(50)	(50)	(49)
Stomach, forestomach	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell papilloma, multiple		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma		2 (4%)	
Adrenal medulla	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Pheochromocytoma benign		4 (8%)	
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)		2 (4%)
Parathyroid gland	(42)	(46)	(45)
Adenoma	1 (2%)		
Pituitary gland	(50)	(49)	(50)
Pars distalis, adenoma	27 (54%)	26 (53%)	24 (48%)
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	4 (8%)	3 (6%)	6 (12%)
C-cell, carcinoma	1 (2%)	2 (4%)	2 (4%)
Follicular cell, adenoma	2 (4%)		
Follicular cell, carcinoma	1 (2%)	1 (2%)	
General Body System			
None			

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

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System			
Clitoral gland	(49)	(50)	(50)
Adenoma	7 (14%)	5 (10%)	4 (8%)
Carcinoma	1 (2%)	6 (12%)	2 (4%)
Bilateral, adenoma	1 (2%)		
Bilateral, carcinoma	1 (2%)	2 (4%)	2 (4%)
Ovary	(50)	(50)	(50)
Granulosa-theca tumor malignant	1 (2%)		
Granulosa-theca tumor benign			1 (2%)
Histiocytic sarcoma	1 (2%)		
Uterus	(50)	(50)	(50)
Deciduoma benign			1 (2%)
Leiomyosarcoma		1 (2%)	
Polyp stromal	6 (12%)	6 (12%)	5 (10%)
Sarcoma stromal			1 (2%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(41)	(36)	(36)
Mediastinal, histiocytic sarcoma	1 (2%)		
Lymph node, mandibular	(50)	(48)	(47)
Lymph node, mesenteric	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Spleen	(50)	(50)	(50)
Thymus	(47)	(50)	(49)
Histiocytic sarcoma	1 (2%)		
Thymoma benign			1 (2%)
Integumentary System			
Mammary gland	(49)	(50)	(50)
Adenoma	1 (2%)		
Carcinoma	2 (4%)	1 (2%)	2 (4%)
Carcinoma, multiple		1 (2%)	
Fibroadenoma	17 (35%)	14 (28%)	3 (6%)
Fibroadenoma, multiple	1 (2%)	2 (4%)	
Skin	(50)	(50)	(50)
Squamous cell papilloma, multiple			1 (2%)
Sebaceous gland, skin, site of application, adenoma		1 (2%)	
Subcutaneous tissue, histiocytic sarcoma	1 (2%)		
Subcutaneous tissue, pinna, melanoma malignant	1 (2%)		
Subcutaneous tissue, skin, site of application, fibrosarcoma			1 (2%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Femur, osteosarcoma	1 (2%)		
Skeletal muscle	(3)	(1)	
Histiocytic sarcoma	1 (33%)		
Osteosarcoma, metastatic, bone	1 (33%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Granulosa-theca tumor malignant, metastatic, ovary	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Renal tubule, carcinoma		2 (4%)	
Urinary bladder	(50)	(50)	(50)
Papilloma		1 (2%)	
Transitional epithelium, papilloma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Leukemia mononuclear	10 (20%)	9 (18%)	4 (8%)
Lymphoma malignant		2 (4%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]	48	43	37
Total primary neoplasms	89	93	65
Total animals with benign neoplasms	43	39	34
Total benign neoplasms	69	66	50
Total animals with malignant neoplasms	19	20	15
Total malignant neoplasms	20	27	15
Total animals with metastatic neoplasms	2		
Total metastatic neoplasms	3		

[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 Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	342	493	522	552	585	606	613	613	618	619	632	636	639	655	669	680	697	698	708	717	723	727	728	728	728
Carcass ID Number	180	177	163	187	195	184	157	161	182	159	151	197	194	156	193	174	188	164	165	169	172	181	162	166	178
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Mesentery							+				+						+								
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X	X	X			X	X	X					X	X		X	X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma								X																	
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																									
Bilateral, adenoma																X									
Bilateral, carcinoma															X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																						X			
Histiocytic sarcoma		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X									X											

+: 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 Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	185	192	198	152	153	154	155	158	160	167	168	170	171	173	175	176	179	183	186	189	190	191	196	199	200	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery																+										4
Oral mucosa																+										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth								+																		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	M	M	M	+	42
Adenoma	X																									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X				X			X			X	X	X		X	X	X	X		X	27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X	X												X				X				4
C-cell, carcinoma																					X					1
Follicular cell, adenoma								X																		2
Follicular cell, carcinoma																	X									1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X			X	X						X					X					X			7
Carcinoma																		X								1
Bilateral, adenoma																										1
Bilateral, carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X									X		X								X					6

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

Number of Days on Study	342	493	522	552	585	606	613	613	618	619	632	636	639	655	669	680	697	698	708	717	723	727	728	728	728
Carcass ID Number	180	177	163	187	195	184	157	161	182	159	151	197	194	156	193	174	188	164	165	169	172	181	162	166	178
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+		+	+	+	+	+	+	+	+	+	+		+		+	+		+	+		+
Mediastinal, histiocytic sarcoma		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Histiocytic sarcoma		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																							X		
Fibroadenoma									X									X	X		X			X	
Fibroadenoma, multiple															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma		X																							
Subcutaneous tissue, pinna, melanoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma													X												
Skeletal muscle		+											+	+											
Histiocytic sarcoma		X																							
Osteosarcoma, metastatic, bone													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary																						X			
Histiocytic sarcoma		X																							
Osteosarcoma, metastatic, bone													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+			+				+					+	+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																							X		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Leukemia mononuclear									X	X					X		X			X					

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

Number of Days on Study	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	185	192	198	152	153	154	155	158	160	167	168	170	171	173	175	176	179	183	186	189	190	191	196	199	200	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+			41
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X																				1
Carcinoma							X																			2
Fibroadenoma	X		X			X		X	X			X	X	X	X					X		X		X		17
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, pinna, melanoma malignant															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Skeletal muscle																										3
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye														+												6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear			X					X								X			X				X			10

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

Number of Days on Study	225	271	280	382	390	408	476	514	533	533	562	578	578	582	585	612	637	651	677	689	689	692	708	712	719
Carcass ID Number	224	223	248	215	203	243	219	210	208	213	228	207	225	234	226	242	205	244	245	209	220	216	237	232	233
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+							+															
Oral mucosa									+																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma, multiple																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X					X		X	X	X		X	X	X	X	X		X	X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma													X												
Bilateral, carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Polyp stromal																				X					

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

Number of Days on Study	722	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	201	202	206	214	217	222	229	249	204	211	212	218	221	227	230	231	235	236	238	239	240	241	246	247	250	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+								+				+							5
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma, multiple																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X						X							2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign											X	X								X						4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X				X			X	X				X		X	X		X	X	X	X		X	X		26
Pars intermedia, adenoma										X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X			X					X														3
C-cell, carcinoma					X																	X				2
Follicular cell, carcinoma					X																					1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X							X		X			X		5
Carcinoma					X				X									X				X			X	6
Bilateral, carcinoma		X				X																				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma					X																					1
Polyp stromal					X									X							X	X	X			6

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

Number of Days on Study	225	271	280	382	390	408	476	514	533	533	562	578	578	582	585	612	637	651	677	689	689	692	708	712	719
Carcass ID Number	224	223	248	215	203	243	219	210	208	213	228	207	225	234	226	242	205	244	245	209	220	216	237	232	233
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+			+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, multiple																									
Fibroadenoma													X			X				X	X		X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, skin, site of application, adenoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																		+							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X						X			X											X		
Lymphoma malignant										X															

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

Number of Days on Study	722	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	201	202	206	214	217	222	229	249	204	211	212	218	221	227	230	231	235	236	238	239	240	241	246	247	250	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+			+		+		+		+	+		+	+	+	+	+	+	+	+		+	36
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X														1
Carcinoma, multiple																		X								1
Fibroadenoma	X		X			X						X			X	X	X					X				14
Fibroadenoma, multiple		X																X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, skin, site of application, adenoma 1																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+																					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																	X									2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																								X		1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X				X	X			X									X			9
Lymphoma malignant																		X								2

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

Number of Days on Study	271	294	308	314	373	374	377	387	466	479	522	536	537	545	557	588	620	626	639	665	666	669	672	689	702
Carcass ID Number	293	275	280	277	258	283	272	267	264	287	298	263	294	276	290	288	262	257	286	274	284	260	265	253	299
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery														+											
Oral mucosa																									+
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X	X		X		X	X	X	X		X		X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
C-cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma												X													
Bilateral, carcinoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign					X																				
Polyp stromal																				X					X
Sarcoma stromal									X																
Vagina					+											+									

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

Number of Days on Study	715	718	724	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	255	256	251	259	269	271	273	278	281	289	291	292	295	254	261	266	268	270	279	282	285	295	296	297	300	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																					X					1
Mesentery																			+							2
Oral mucosa								+					+													3
Gingival, squamous cell carcinoma								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma										X																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																					+					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X										X	2
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X				X	X		X		X				X	X		X	X			X	X	X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X					X			X	X								X				6
C-cell, carcinoma	X																									2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X																	X						4
Carcinoma									X																	2
Bilateral, carcinoma																X										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma benign																										1
Polyp stromal											X								X		X					5
Sarcoma stromal																										1
Vagina																										2

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

Number of Days on Study	271	294	308	314	373	374	377	387	466	479	522	536	537	545	557	588	620	626	639	665	666	669	672	689	702
Carcass ID Number	293	275	280	277	258	283	272	267	264	287	298	263	294	276	290	288	262	257	286	274	284	260	265	253	299
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+					+	+			+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																							X		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma, multiple																									
Subcutaneous tissue, skin, site of application, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+						+											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X		

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

Number of Days on Study	715	718	724	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	255	256	251	259	269	271	273	278	281	289	291	292	252	254	261	266	268	270	279	282	285	295	296	297	300	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+			+		+	+	36
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X				X									2
Fibroadenoma																						X		X		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma, multiple									X																	1
Subcutaneous tissue, skin, site of application, fibrosarcoma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+																		+		+					5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																						X		X	X	4

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate[b]	0.0%	10.6%	0.0%
Terminal rate[c]	0/28 (0%)	3/24 (13%)	0/22 (0%)
First incidence (days)	—[e]	677	—
Poly-3 test[d]	P=0.516	P=0.046	—[f]
Clitoral Gland: Adenoma			
Overall rate	8/49 (16%)	5/50 (10%)	4/50 (8%)
Adjusted rate	19.1%	13.1%	11.1%
Terminal rate	6/28 (21%)	4/24 (17%)	1/22 (5%)
First incidence (days)	680	578	669
Poly-3 test	P=0.200N	P=0.338N	P=0.259N
Clitoral Gland: Carcinoma			
Overall rate	2/49 (4%)	8/50 (16%)	4/50 (8%)
Adjusted rate	4.8%	21.0%	11.0%
Terminal rate	1/28 (4%)	7/24 (29%)	2/22 (9%)
First incidence (days)	669	578	536
Poly-3 test	P=0.197	P=0.029	P=0.272
Clitoral Gland: Adenoma or Carcinoma			
Overall rate	9/49 (18%)	13/50 (26%)	8/50 (16%)
Adjusted rate	21.3%	33.6%	21.8%
Terminal rate	6/28 (21%)	11/24 (46%)	3/22 (14%)
First incidence (days)	669	578	536
Poly-3 test	P=0.487	P=0.158	P=0.587
Kidney: Adenoma or Carcinoma (Step Sections)			
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	8.0%	2.8%
Terminal rate	0/28 (0%)	3/24 (13%)	1/22 (5%)
First incidence (days)	—	728 (T)	728 (T)
Poly-3 test	P=0.298	P=0.097	P=0.464
Kidney: Adenoma or Carcinoma (Single and Step Sections)			
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	0.0%	10.6%	2.8%
Terminal rate	0/28 (0%)	3/24 (13%)	1/22 (5%)
First incidence (days)	—	719	728 (T)
Poly-3 test	P=0.293	P=0.045	P=0.464
Mammary Gland: Fibroadenoma			
Overall rate	18/50 (36%)	16/50 (32%)	3/50 (6%)
Adjusted rate	41.4%	41.0%	8.4%
Terminal rate	13/28 (46%)	9/24 (38%)	2/22 (9%)
First incidence (days)	618	578	669
Poly-3 test	P<0.001N	P=0.577N	P<0.001N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	18/50 (36%)	16/50 (32%)	3/50 (6%)
Adjusted rate	41.4%	41.0%	8.4%
Terminal rate	13/28 (46%)	9/24 (38%)	2/22 (9%)
First incidence (days)	618	578	669
Poly-3 test	P<0.001N	P=0.577N	P<0.001N
Mammary Gland: Adenoma or Carcinoma			
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	7.0%	5.3%	5.6%
Terminal rate	3/28 (11%)	2/24 (8%)	2/22 (9%)
First incidence (days)	728 (T)	728 (T)	728 (T)
Poly-3 test	P=0.490N	P=0.557N	P=0.582N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	20/50 (40%)	16/50 (32%)	5/50 (10%)
Adjusted rate	46.0%	41.0%	14.0%
Terminal rate	15/28 (54%)	9/24 (38%)	4/22 (18%)
First incidence (days)	618	578	669
Poly-3 test	P=0.002N	P=0.407N	P=0.002N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	27/50 (54%)	26/49 (53%)	24/50 (48%)
Adjusted rate	58.3%	62.2%	60.0%
Terminal rate	15/28 (54%)	12/24 (50%)	11/22 (50%)
First incidence (days)	522	382	479
Poly-3 test	P=0.471	P=0.437	P=0.524
Thyroid Gland (C-cell): Adenoma			
Overall rate	4/50 (8%)	3/50 (6%)	6/50 (12%)
Adjusted rate	9.4%	8.0%	16.7%
Terminal rate	4/28 (14%)	3/24 (13%)	5/22 (23%)
First incidence (days)	728 (T)	728 (T)	626
Poly-3 test	P=0.224	P=0.568N	P=0.266
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	5/50 (10%)	5/50 (10%)	8/50 (16%)
Adjusted rate	11.7%	13.3%	22.1%
Terminal rate	5/28 (18%)	5/24 (21%)	5/22 (23%)
First incidence (days)	728 (T)	728 (T)	626
Poly-3 test	P=0.142	P=0.550	P=0.174
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.0%	2.7%	0.0%
Terminal rate	2/28 (7%)	1/24 (4%)	0/22 (0%)
First incidence (days)	613	728 (T)	—
Poly-3 test	P=0.083N	P=0.355N	P=0.156N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Uterus: Stromal Polyp			
Overall rate	6/50 (12%)	6/50 (12%)	5/50 (10%)
Adjusted rate	13.8%	15.9%	13.9%
Terminal rate	4/28 (14%)	5/24 (21%)	3/22 (14%)
First incidence (days)	585	689	665
Poly-3 test	P=0.553	P=0.521	P=0.622
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rate	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted rate	13.8%	15.9%	16.4%
Terminal rate	4/28 (14%)	5/24 (21%)	3/22 (14%)
First incidence (days)	585	689	466
Poly-3 test	P=0.437	P=0.521	P=0.499
All Organs: Mononuclear Cell Leukemia			
Overall rate	10/50 (20%)	9/50 (18%)	4/50 (8%)
Adjusted rate	22.8%	22.6%	11.2%
Terminal rate	5/28 (18%)	5/24 (21%)	3/22 (14%)
First incidence (days)	618	280	672
Poly-3 test	P=0.141N	P=0.595N	P=0.144N
All Organs: Benign Neoplasms			
Overall rate	43/50 (86%)	39/50 (78%)	34/50 (68%)
Adjusted rate	89.8%	91.3%	82.8%
Terminal rate	26/28 (93%)	23/24 (96%)	19/22 (86%)
First incidence (days)	522	382	373
Poly-3 test	P=0.187N	P=0.558	P=0.235N
All Organs: Malignant Neoplasms			
Overall rate	19/50 (38%)	20/50 (40%)	15/50 (30%)
Adjusted rate	42.4%	48.9%	40.0%
Terminal rate	11/28 (39%)	13/24 (54%)	9/22 (41%)
First incidence (days)	493	280	466
Poly-3 test	P=0.497N	P=0.347	P=0.505N
All Organs: Benign or Malignant Neoplasms			
Overall rate	48/50 (96%)	43/50 (86%)	37/50 (74%)
Adjusted rate	97.8%	95.8%	86.9%
Terminal rate	27/28 (96%)	24/24 (100%)	19/22 (86%)
First incidence (days)	493	280	373
Poly-3 test	P=0.015N	P=0.522N	P=0.038N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, 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
[f] Value of statistic cannot be computed.

TABLE B4
Historical Incidence of Renal Tubule Neoplasms in Vehicle Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Benzethonium Chloride	0/51	0/51	0/51
Coconut Oil Acid Diethanolamine Condensate	0/50	0/50	0/50
Diethanolamine	0/50	0/50	0/50
Lauric Acid Diethanolamine Condensate	1/50	0/50	1/50
Oleic Acid Diethanolamine Condensate	0/50	0/50	0/50
Sodium Xylenesulfonate	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/301 (0.3%)	0/301 (0.0%)	1/301 (0.3%)
Mean ± standard deviation	0.3% ± 0.8%		0.3% ± 0.8%
Range	0%-2%		0%-2%

[a] Data as of 12 July 2000

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

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	7	15	10
Natural deaths	15	11	18
Survivors			
Died last week of study			1
Terminal sacrifice	28	24	21
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Perforation			1 (2%)
Intestine large, colon	(50)	(50)	(50)
Parasite metazoan	2 (4%)	5 (10%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)
Parasite metazoan	6 (12%)	4 (8%)	6 (12%)
Intestine large, cecum	(50)	(50)	(50)
Parasite metazoan	2 (4%)		
Intestine small, duodenum	(50)	(50)	(50)
Epithelium, ulcer			1 (2%)
Intestine small, jejunum	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	
Intestine small, ileum	(50)	(49)	(49)
Inflammation, chronic active		1 (2%)	
Liver	(50)	(50)	(50)
Basophilic focus	31 (62%)	17 (34%)	4 (8%)
Clear cell focus	5 (10%)	4 (8%)	1 (2%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	
Hepatodiaphragmatic nodule	10 (20%)	11 (22%)	14 (28%)
Inflammation, chronic	29 (58%)	26 (52%)	13 (26%)
Mixed cell focus	1 (2%)	2 (4%)	
Pigmentation, hemosiderin	1 (2%)		
Vacuolization cytoplasmic	23 (46%)	20 (40%)	22 (44%)
Bile duct, hyperplasia	26 (52%)	21 (42%)	16 (32%)
Hepatocyte, degeneration, cystic			1 (2%)
Hepatocyte, hyperplasia, adenomatous	1 (2%)	1 (2%)	
Hepatocyte, necrosis	1 (2%)	2 (4%)	
Hepatocyte, centrilobular, degeneration	2 (4%)	1 (2%)	2 (4%)
Hepatocyte, centrilobular, necrosis	1 (2%)		
Serosa, necrosis, fibrinoid	1 (2%)		
Mesentery	(4)	(5)	(2)
Fat, inflammation, chronic active			1 (50%)
Fat, necrosis	3 (75%)	4 (80%)	1 (50%)
Oral mucosa	(1)	(1)	(3)
Gingival, hyperplasia, squamous	1 (100%)		
Gingival, inflammation, chronic active			1 (33%)
Pharyngeal, hyperplasia, squamous		1 (100%)	1 (33%)

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

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

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Pancreas	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
Acinus, atrophy	19 (38%)	13 (26%)	11 (22%)
Stomach, forestomach	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic active	1 (2%)	3 (6%)	10 (20%)
Mineralization		1 (2%)	
Epithelium, hyperplasia	2 (4%)	5 (10%)	13 (26%)
Epithelium, ulcer	1 (2%)	3 (6%)	11 (22%)
Stomach, glandular	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Epithelium, erosion		1 (2%)	1 (2%)
Epithelium, hyperplasia			1 (2%)
Epithelium, ulcer	1 (2%)		
Glands, hyperplasia			1 (2%)
Tongue			(1)
Hyperplasia, squamous			1 (100%)
Tooth	(1)		
Inflammation, chronic active	1 (100%)		
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Aorta, mineralization		1 (2%)	1 (2%)
Pulmonary artery, mineralization			1 (2%)
Heart	(50)	(50)	(50)
Cardiomyopathy, chronic	22 (44%)	16 (32%)	14 (28%)
Inflammation, chronic active	1 (2%)		
Mineralization	1 (2%)		1 (2%)
Atrium, thrombosis		1 (2%)	3 (6%)
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Atrophy		1 (2%)	
Degeneration, cystic	8 (16%)	6 (12%)	8 (16%)
Degeneration, fatty	22 (44%)	14 (28%)	16 (32%)
Fibrosis	1 (2%)		
Hyperplasia	22 (44%)	14 (28%)	11 (22%)
Hypertrophy	10 (20%)	3 (6%)	7 (14%)
Necrosis	1 (2%)		
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	1 (2%)	2 (4%)	3 (6%)
Parathyroid gland	(42)	(46)	(45)
Hyperplasia		1 (2%)	3 (7%)
Pituitary gland	(50)	(49)	(50)
Pars distalis, cyst	23 (46%)	27 (55%)	17 (34%)
Pars distalis, hyperplasia	20 (40%)	19 (39%)	19 (38%)
Pars intermedia, cyst	1 (2%)	2 (4%)	2 (4%)
Thyroid gland	(50)	(50)	(50)
Ectopic thymus		1 (2%)	
C-cell, hyperplasia	17 (34%)	7 (14%)	7 (14%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
General Body System			
None			
Genital System			
Clitoral gland	(49)	(50)	(50)
Hyperplasia	4 (8%)	1 (2%)	3 (6%)
Inflammation, chronic active	6 (12%)	6 (12%)	8 (16%)
Bilateral, duct, cyst			1 (2%)
Duct, cyst	2 (4%)	1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)
Cyst	7 (14%)	8 (16%)	8 (16%)
Uterus	(50)	(50)	(50)
Dysplasia	1 (2%)		
Inflammation, suppurative		1 (2%)	
Endometrium, hyperplasia, cystic		1 (2%)	
Vagina			(2)
Inflammation, suppurative			1 (50%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Atrophy	1 (2%)		
Hyperplasia	12 (24%)	14 (28%)	10 (20%)
Lymph node	(41)	(36)	(36)
Pigmentation, hemosiderin	1 (2%)		
Inguinal, ectasia	1 (2%)		
Mediastinal, congestion			1 (3%)
Mediastinal, pigmentation, hemosiderin	38 (93%)	35 (97%)	34 (94%)
Lymph node, mandibular	(50)	(48)	(47)
Pigmentation, hemosiderin	1 (2%)		
Spleen	(50)	(50)	(50)
Congestion			1 (2%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	3 (6%)	4 (8%)	1 (2%)
Necrosis	1 (2%)		
Pigmentation, hemosiderin	1 (2%)		
Capsule, fibrosis			1 (2%)
Capsule, inflammation, granulomatous	1 (2%)		
Integumentary System			
Mammary gland	(49)	(50)	(50)
Cyst		3 (6%)	
Hyperplasia, cystic	44 (90%)	40 (80%)	40 (80%)
Skin	(50)	(50)	(50)
Cyst epithelial inclusion		2 (4%)	
Inflammation, chronic active		1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)	
Epidermis, hyperplasia		1 (2%)	
Epidermis, skin, site of application, hyperkeratosis	3 (6%)	45 (90%)	47 (94%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System (continued)			
Skin (continued)	(50)	(50)	(50)
Epidermis, skin, site of application, hyperplasia	3 (6%)	46 (92%)	50 (100%)
Epidermis, skin, site of application, parakeratosis	1 (2%)	11 (22%)	23 (46%)
Epidermis, skin, site of application, ulcer	2 (4%)		9 (18%)
Sebaceous gland, skin, site of application, hyperplasia	2 (4%)	46 (92%)	49 (98%)
Skin, site of application, inflammation, chronic active	3 (6%)		6 (12%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy		2 (4%)	2 (4%)
Osteopetrosis	2 (4%)	2 (4%)	
Skeletal muscle	(3)	(1)	
Inflammation, chronic active	1 (33%)		
Nervous System			
Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Spinal cord		(1)	
Hemorrhage		1 (100%)	
Respiratory System			
Lung	(50)	(50)	(50)
Congestion		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, chronic active	7 (14%)	16 (32%)	9 (18%)
Inflammation, granulomatous	3 (6%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	1 (2%)	3 (6%)
Alveolus, infiltration cellular, histiocyte	22 (44%)	24 (48%)	28 (56%)
Mediastinum, necrosis	1 (2%)		
Nose	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	4 (8%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative	4 (8%)	3 (6%)	3 (6%)
Respiratory epithelium, hyperplasia	1 (2%)	4 (8%)	3 (6%)
Respiratory epithelium, metaplasia, squamous		1 (2%)	2 (4%)
Vein, turbinate, septum, thrombosis	1 (2%)		
Special Senses System			
Eye	(6)	(2)	(5)
Anterior chamber, cornea, iris, synechia	1 (17%)		
Bilateral, inflammation, suppurative			1 (20%)
Cornea, inflammation, chronic	1 (17%)		
Lens, cataract	5 (83%)	1 (50%)	4 (80%)
Retina, atrophy	3 (50%)	1 (50%)	3 (60%)

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

	Vehicle Control	50 mg/kg	100 mg/kg
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet	2 (4%)		
Cyst	2 (4%)		1 (2%)
Mineralization	50 (100%)	45 (90%)	47 (94%)
Nephropathy, chronic	47 (94%)	46 (92%)	46 (92%)
Pigmentation, hemosiderin	48 (96%)	46 (92%)	47 (94%)
Renal tubule, hyperplasia	2 (4%)	8 (16%)	15 (30%)
Urinary bladder	(50)	(50)	(50)
Transitional epithelium, hyperplasia		1 (2%)	2 (4%)

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	5	7	7
Natural deaths	4	6	7
Survivors			
Terminal sacrifice	41	37	36
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)
Intestine small, duodenum	(49)	(50)	(50)
Hepatoblastoma, metastatic, liver	1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Liver	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Hemangioma			1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	
Hemangiosarcoma, multiple	1 (2%)		1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)		1 (2%)
Hepatoblastoma		1 (2%)	10 (20%)
Hepatoblastoma, multiple	1 (2%)		
Hepatocellular carcinoma	7 (14%)	10 (20%)	12 (24%)
Hepatocellular carcinoma, multiple	5 (10%)	2 (4%)	8 (16%)
Hepatocellular adenoma	11 (22%)	11 (22%)	4 (8%)
Hepatocellular adenoma, multiple	11 (22%)	24 (48%)	41 (82%)
Histiocytic sarcoma	1 (2%)	2 (4%)	
Mast cell tumor malignant, metastatic, skin			1 (2%)
Mesentery	(3)	(3)	(4)
Hepatoblastoma, metastatic, liver	1 (33%)		
Hepatoblastoma, metastatic, pancreas			1 (25%)
Histiocytic sarcoma	1 (33%)	1 (33%)	
Oral mucosa		(1)	
Gingival, squamous cell carcinoma		1 (100%)	
Pancreas	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver	1 (2%)		
Hepatoblastoma, metastatic, pancreas			1 (2%)
Salivary glands	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Hemangioma			1 (2%)
Squamous cell papilloma			2 (4%)
Stomach, glandular	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma		1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Cardiovascular System			
Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)	
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	
Pituitary gland	(45)	(47)	(49)
Pars distalis, adenoma			1 (2%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)	
General Body System			
None			
Genital System			
Ductus deferens		(1)	
Epididymis	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
Preputial gland	(49)	(50)	(50)
Prostate	(50)	(50)	(50)
Seminal vesicle	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)
Histiocytic sarcoma	1 (2%)		
Testes	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)	1 (2%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, spleen	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Lymph node	(2)	(5)	(1)
Lumbar, alveolar/bronchiolar carcinoma, metastatic, lung		1 (20%)	
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (20%)	
Mediastinal, histiocytic sarcoma		1 (20%)	
Lymph node, mandibular	(47)	(45)	(44)
Lymph node, mesenteric	(46)	(48)	(47)
Hepatoblastoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)	
Spleen	(50)	(50)	(50)
Hemangiosarcoma	3 (6%)		1 (2%)
Hepatoblastoma, metastatic, liver	1 (2%)		
Thymus	(43)	(44)	(41)
Histiocytic sarcoma		1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Integumentary System			
Skin	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
Melanoma malignant			1 (2%)
Skin, site of application, mast cell tumor malignant			1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)		
Musculoskeletal System			
Bone	(50)	(50)	(50)
Vertebra, osteosarcoma			1 (2%)
Skeletal muscle		(1)	(3)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)	
Hepatoblastoma, metastatic, pancreas			1 (33%)
Nervous System			
Brain	(50)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	7 (14%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)	5 (10%)	2 (4%)
Hepatoblastoma, metastatic, liver	1 (2%)		3 (6%)
Hepatoblastoma, metastatic, pancreas			1 (2%)
Hepatocellular carcinoma, metastatic, liver	6 (12%)	2 (4%)	4 (8%)
Histiocytic sarcoma		2 (4%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Serosa, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Nose	(50)	(50)	(50)
Special Senses System			
Eye	(1)	(2)	(1)
Sarcoma	1 (100%)		
Harderian gland	(3)	(3)	(6)
Adenoma	2 (67%)		
Carcinoma		2 (67%)	3 (50%)
Bilateral, carcinoma		1 (33%)	1 (17%)
Urinary System			
Kidney	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Hepatoblastoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant, metastatic, skin			1 (2%)
Renal tubule, adenoma	1 (2%)	1 (2%)	7 (14%)
Renal tubule, carcinoma			2 (4%)
Urinary bladder	(50)	(50)	(50)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	
Lymphoma malignant	2 (4%)	3 (6%)	3 (6%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	35	45	50
Total primary neoplasms	65	80	113
Total animals with benign neoplasms	26	39	47
Total benign neoplasms	38	49	65
Total animals with malignant neoplasms	22	28	35
Total malignant neoplasms	27	31	48
Total animals with metastatic neoplasms	9	3	12
Total metastatic neoplasms	17	9	16

[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 Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	420	490	584	612	618	645	664	673	700	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	729
Carcass ID Number	050	002	009	006	020	030	007	031	035	055	011	018	022	026	001	012	016	017	027	029	034	038	045	047	003
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver							X																		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Hemangiosarcoma, multiple	X																								
Hemangiosarcoma, metastatic, spleen																							X		
Hepatoblastoma, multiple							X																		
Hepatocellular carcinoma									X										X	X					
Hepatocellular carcinoma, multiple			X					X		X	X											X			
Hepatocellular adenoma				X	X					X						X				X			X		X
Hepatocellular adenoma, multiple						X			X										X						
Histiocytic sarcoma					X																				
Mesentery					+		+																		
Hepatoblastoma, metastatic, liver							X																		
Histiocytic sarcoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver							X																		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Parathyroid gland	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	004	008	010	013	014	015	019	021	023	024	025	028	032	033	036	037	039	040	041	042	043	044	046	048	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma, metastatic, liver																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hemangiosarcoma, metastatic, spleen																										1
Hepatoblastoma, multiple																										1
Hepatocellular carcinoma								X				X		X						X						7
Hepatocellular carcinoma, multiple																										5
Hepatocellular adenoma				X						X		X	X													11
Hepatocellular adenoma, multiple														X			X	X	X		X		X	X	X	11
Histiocytic sarcoma																										1
Mesentery																		+								3
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	43
Pituitary gland	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars intermedia, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

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

Number of Days on Study	420	490	584	612	618	645	664	673	700	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	729
Carcass ID Number	050	002	009	006	020	030	007	031	035	055	011	018	022	026	001	012	016	017	027	029	034	038	045	047	003
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver	X																								
Hemangiosarcoma, metastatic, spleen																							X		
Lymph node				+																					
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Hepatoblastoma, metastatic, liver							X																		
Histiocytic sarcoma					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X											X		
Hepatoblastoma, metastatic, liver							X																		
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X			X						X	X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																				X			X		
Alveolar/bronchiolar carcinoma, multiple																									
Hepatoblastoma, metastatic, liver							X																		
Hepatocellular carcinoma, metastatic, liver								X	X	X									X			X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Sarcoma																									
Harderian gland																					+	+			
Adenoma																					X	X			

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	004	008	010	013	014	015	019	021	023	024	025	028	032	033	036	037	039	040	041	042	043	044	046	048	049	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Hemangiosarcoma, metastatic, spleen																										1
Lymph node				+																						2
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						3
Hepatoblastoma, metastatic, liver																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X			X	X				X	X				X			10
Alveolar/bronchiolar adenoma, multiple																	X									1
Alveolar/bronchiolar carcinoma								X																		3
Alveolar/bronchiolar carcinoma, multiple											X															1
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver								X																		6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																									+	1
Sarcoma																									X	1
Harderian gland	+																								M	3
Adenoma																										2

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

Number of Days on Study	420	490	584	612	618	645	664	673	700	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	729
Carcass ID Number	050	002	009	006	020	030	007	031	335	055	011	118	022	026	001	012	116	117	227	229	034	038	045	047	040	003
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver							X																			
Renal tubule, adenoma												X														
Ureter							+																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																					
Lymphoma malignant				X																						

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	004	008	010	013	014	015	019	021	023	024	025	028	032	033	036	037	039	040	041	042	043	044	046	048	049	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Renal tubule, adenoma																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant				X																						2

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

Number of Days on Study	304	356	454	507	576	617	645	652	653	653	692	696	711	727	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	086	085	070	063	067	099	089	076	051	088	095	072	082	055	059	060	061	065	071	078	083	084	098	010	052
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Hemangiosarcoma																X									
Hepatoblastoma				X																					
Hepatocellular carcinoma						X		X					X							X		X		X	
Hepatocellular carcinoma, multiple					X						X														
Hepatocellular adenoma																X	X	X	X	X	X				
Hepatocellular adenoma, multiple				X		X	X		X	X			X	X	X							X	X	X	
Histiocytic sarcoma			X									X													
Mesentery												+													
Histiocytic sarcoma												X													
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Tooth																							+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Histiocytic sarcoma			X																						
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	+	M	+	M	+	+	M	M	M	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma															X										
General Body System																									
None																									

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

Number of Days on Study	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	054	066	068	069	077	092	093	094	053	056	057	058	062	064	073	074	075	079	080	081	087	090	091	096	097	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
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma																				X						2
Hepatoblastoma																										1
Hepatocellular carcinoma	X					X										X								X		10
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma					X			X				X							X	X						11
Hepatocellular adenoma, multiple	X	X		X		X	X			X	X			X	X	X	X	X				X				24
Histiocytic sarcoma																										2
Mesentery																			+				+			3
Histiocytic sarcoma																										1
Oral mucosa					+																					1
Gingival, squamous cell carcinoma					X																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

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

Number of Days on Study	304	356	454	507	576	617	645	652	653	653	692	696	711	727	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	086	085	070	063	067	099	089	076	051	088	095	072	082	055	059	060	061	065	071	078	083	084	098	010	052
Genital System																									
Ductus deferens							+																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymph node	+						+		+			+													
Lumbar, alveolar/bronchiolar carcinoma, metastatic, lung									X																
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung									X																
Mediastinal, histiocytic sarcoma												X													
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+
Histiocytic sarcoma												X													
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X					X				X							X		
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma															X										
Alveolar/bronchiolar carcinoma, multiple									X	X															
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma			X									X													
Serosa, alveolar/bronchiolar carcinoma, metastatic, lung									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	054	066	068	069	077	092	093	094	053	056	057	058	062	064	073	074	075	079	080	081	087	090	091	096	097	Total Tissues/ Tumors
Genital System																										
Ductus deferens																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																	X									1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																							+			5
Lumbar, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X		X											X			7
Alveolar/bronchiolar adenoma, multiple									X													X				3
Alveolar/bronchiolar carcinoma															X											2
Alveolar/bronchiolar carcinoma, multiple	X				X								X													5
Hepatocellular carcinoma, metastatic, liver						X										X										2
Histiocytic sarcoma																										2
Serosa, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	304	356	454	507	576	617	645	652	653	653	692	696	711	727	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	086	085	070	063	067	099	089	076	051	088	095	072	082	055	059	060	061	065	071	078	083	084	098	090	052
Special Senses System																									
Eye																									
Harderian gland																	+								
Carcinoma																	X								
Bilateral, carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Histiocytic sarcoma			X																						
Renal tubule, adenoma																				X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X									X													
Lymphoma malignant	X						X																		

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

Number of Days on Study	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	054	066	068	069	077	092	093	094	053	056	057	058	062	064	073	074	075	079	080	081	087	090	091	096	097	Total Tissues/ Tumors
Special Senses System																										
Eye						+	+																			2
Harderian gland						+	+																			3
Carcinoma						X																				2
Bilateral, carcinoma							X																			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant																							X			3

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

Number of Days on Study	401	456	505	555	595	597	630	662	667	692	692	710	713	722	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	125	110	122	146	127	132	118	145	120	119	150	124	107	141	111	112	113	117	123	129	130	131	133	134	102
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma, multiple																									X
Hemangiosarcoma, metastatic, spleen																									
Hepatoblastoma										X			X			X				X				X	
Hepatocellular carcinoma		X			X											X									
Hepatocellular carcinoma, multiple										X		X		X	X									X	
Hepatocellular adenoma	X			X		X										X									
Hepatocellular adenoma, multiple		X			X		X	X	X	X	X		X		X		X	X	X		X	X	X	X	X
Mast cell tumor malignant, metastatic, skin																									
Mesentery					+																				
Hepatoblastoma, metastatic, pancreas																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, pancreas																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Squamous cell papilloma												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	103	105	114	135	137	139	140	101	104	106	108	109	115	116	121	126	128	136	138	142	143	144	147	148	149	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																			1
Hemangiosarcoma, multiple																										1
Hemangiosarcoma, metastatic, spleen																								X		1
Hepatoblastoma	X		X								X	X						X								10
Hepatocellular carcinoma		X		X	X							X	X	X			X		X	X						12
Hepatocellular carcinoma, multiple																		X			X				X	8
Hepatocellular adenoma																										4
Hepatocellular adenoma, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Mast cell tumor malignant, metastatic, skin																									X	1
Mesentery	+												+						+							4
Hepatoblastoma, metastatic, pancreas	X																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, pancreas	X																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																		X								1
Squamous cell papilloma																	X									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung			X																							1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

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

Number of Days on Study	401	456	505	555	595	597	630	662	667	692	692	710	713	722	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	125	110	122	146	127	132	118	145	120	119	150	124	107	141	111	112	113	117	123	129	130	131	133	134	102
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+																
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																	X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																		+							
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant																									
Skin, site of application, mast cell tumor malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma						X																			
Skeletal muscle																								+	
Hepatoblastoma, metastatic, pancreas																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X	X												X					
Alveolar/bronchiolar adenoma, multiple															X										
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple									X															X	
Hepatoblastoma, metastatic, liver													X			X									
Hepatoblastoma, metastatic, pancreas																									
Hepatocellular carcinoma, metastatic, liver		X												X										X	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	103	105	114	135	137	139	140	101	104	106	108	109	115	116	121	126	128	136	138	142	143	144	147	148	149		Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Penis																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node																											1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																								X			1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+		41
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		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Melanoma malignant																						X					1
Skin, site of application, mast cell tumor malignant																									X		1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Vertebra, osteosarcoma																											1
Skeletal muscle	+										+																3
Hepatoblastoma, metastatic, pancreas	X																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma			X					X									X										6
Alveolar/bronchiolar adenoma, multiple																											1
Alveolar/bronchiolar carcinoma			X																								1
Alveolar/bronchiolar carcinoma, multiple																											2
Hepatoblastoma, metastatic, liver												X															3
Hepatoblastoma, metastatic, pancreas	X																										1
Hepatocellular carcinoma, metastatic, liver																			X								4
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

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

Number of Days on Study	401	456	505	555	595	597	630	662	667	692	692	710	713	722	727	727	727	727	727	727	727	727	727	727	727	728
Carcass ID Number	125	110	122	146	127	132	118	145	120	119	150	124	107	141	111	112	113	117	123	129	130	131	133	134	102
Special Senses System																										
Eye							+																			
Harderian gland			+				+			+				+												
Carcinoma							X			X																
Bilateral, carcinoma														X												
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin																										
Renal tubule, adenoma						X		X		X																X
Renal tubule, carcinoma																										
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 Coconut Oil Acid Diethanolamine Condensate: 200 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	103	105	114	135	137	139	140	101	104	106	108	109	115	116	121	126	128	136	138	142	143	144	147	148	149	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland																+				+						6
Carcinoma																X										3
Bilateral, carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, skin																									X	1
Renal tubule, adenoma						X			X					X												7
Renal tubule, carcinoma											X											X				2
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																									X	3

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

	Vehicle Control	100 mg/kg	200 mg/kg
Harderian Gland: Carcinoma			
Overall rate[a]	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rate[b]	0.0%	6.8%	8.8%
Terminal rate[c]	0/41 (0%)	3/37 (8%)	1/36 (3%)
First incidence (days)	—[e]	727 (T)	630
Poly-3 test[d]	P=0.045	P=0.111	P=0.058
Harderian Gland: Adenoma or Carcinoma			
Overall rate	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.3%	6.8%	8.8%
Terminal rate	2/41 (5%)	3/37 (8%)	1/36 (3%)
First incidence (days)	727 (T)	727 (T)	630
Poly-3 test	P=0.258	P=0.480	P=0.329
Kidney (Renal Tubule): Adenoma			
Overall rate	1/50 (2%)	1/50 (2%)	7/50 (14%)
Adjusted rate	2.2%	2.3%	15.3%
Terminal rate	1/41 (2%)	1/37 (3%)	4/36 (11%)
First incidence (days)	727 (T)	727 (T)	597
Poly-3 test	P=0.009	P=0.751	P=0.029
Kidney (Renal Tubule): Adenoma or Carcinoma			
Overall rate	1/50 (2%)	1/50 (2%)	9/50 (18%)
Adjusted rate	2.2%	2.3%	19.6%
Terminal rate	1/41 (2%)	1/37 (3%)	6/36 (17%)
First incidence (days)	727 (T)	727 (T)	597
Poly-3 test	P<0.001	P=0.751	P=0.007
Liver: Hepatocellular Adenoma			
Overall rate	22/50 (44%)	35/50 (70%)	45/50 (90%)
Adjusted rate	46.2%	75.4%	91.4%
Terminal rate	18/41 (44%)	29/37 (78%)	34/36 (94%)
First incidence (days)	612	507	401
Poly-3 test	P<0.001	P=0.002	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rate	12/50 (24%)	12/50 (24%)	20/50 (40%)
Adjusted rate	25.4%	26.2%	43.0%
Terminal rate	9/41 (22%)	7/37 (19%)	15/36 (42%)
First incidence (days)	584	576	456
Poly-3 test	P=0.041	P=0.561	P=0.055
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	28/50 (56%)	39/50 (78%)	47/50 (94%)
Adjusted rate	58.0%	82.4%	95.3%
Terminal rate	22/41 (54%)	30/37 (81%)	34/36 (94%)
First incidence (days)	584	507	401
Poly-3 test	P<0.001	P=0.007	P<0.001

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

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatoblastoma			
Overall rate	1/50 (2%)	1/50 (2%)	10/50 (20%)
Adjusted rate	2.1%	2.2%	22.1%
Terminal rate	0/41 (0%)	0/37 (0%)	8/36 (22%)
First incidence (days)	664	507	692
Poly-3 test	P<0.001	P=0.753	P=0.003
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	13/50 (26%)	13/50 (26%)	25/50 (50%)
Adjusted rate	27.4%	28.0%	53.7%
Terminal rate	9/41 (22%)	7/37 (19%)	19/36 (53%)
First incidence (days)	584	507	456
Poly-3 test	P=0.005	P=0.567	P=0.007
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	29/50 (58%)	39/50 (78%)	49/50 (98%)
Adjusted rate	59.8%	82.4%	99.3%
Terminal rate	22/41 (54%)	30/37 (81%)	36/36 (100%)
First incidence (days)	584	507	401
Poly-3 test	P<0.001	P=0.011	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	11/50 (22%)	10/50 (20%)	7/50 (14%)
Adjusted rate	23.7%	22.3%	15.3%
Terminal rate	11/41 (27%)	8/37 (22%)	5/36 (14%)
First incidence (days)	727 (T)	645	630
Poly-3 test	P=0.193N	P=0.535N	P=0.226N
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	4/50 (8%)	7/50 (14%)	3/50 (6%)
Adjusted rate	8.6%	15.6%	6.6%
Terminal rate	4/41 (10%)	5/37 (14%)	2/36 (6%)
First incidence (days)	727 (T)	653	667
Poly-3 test	P=0.451N	P=0.243	P=0.513N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	15/50 (30%)	17/50 (34%)	9/50 (18%)
Adjusted rate	32.3%	37.4%	19.6%
Terminal rate	15/41 (37%)	13/37 (35%)	6/36 (17%)
First incidence (days)	727 (T)	645	630
Poly-3 test	P=0.110N	P=0.385	P=0.122N
Spleen: Hemangiosarcoma			
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.5%	0.0%	2.2%
Terminal rate	3/41 (7%)	0/37 (0%)	1/36 (3%)
First incidence (days)	727 (T)	—	727 (T)
Poly-3 test	P=0.180N	P=0.127N	P=0.316N

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

	Vehicle Control	100 mg/kg	200 mg/kg
All Organs: Hemangiosarcoma			
Overall rate	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted rate	12.5%	4.5%	6.6%
Terminal rate	4/41 (10%)	2/37 (5%)	2/36 (6%)
First incidence (days)	420	727 (T)	555
Poly-3 test	P=0.184N	P=0.159N	P=0.267N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	6/50 (12%)	2/50 (4%)	5/50 (10%)
Adjusted rate	12.5%	4.5%	11.0%
Terminal rate	4/41 (10%)	2/37 (5%)	4/36 (11%)
First incidence (days)	420	727 (T)	555
Poly-3 test	P=0.454N	P=0.159N	P=0.534N
All Organs: Malignant Lymphoma			
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	4.3%	6.6%	6.6%
Terminal rate	1/41 (2%)	1/37 (3%)	2/36 (6%)
First incidence (days)	612	304	505
Poly-3 test	P=0.402	P=0.489	P=0.490
All Organs: Benign Neoplasms			
Overall rate	26/50 (52%)	39/50 (78%)	47/50 (94%)
Adjusted rate	54.7%	83.6%	95.3%
Terminal rate	22/41 (54%)	31/37 (84%)	35/36 (97%)
First incidence (days)	612	507	401
Poly-3 test	P<0.001	P<0.001	P<0.001
All Organs: Malignant Neoplasms			
Overall rate	22/50 (44%)	28/50 (56%)	35/50 (70%)
Adjusted rate	44.3%	57.0%	71.7%
Terminal rate	14/41 (34%)	16/37 (43%)	24/36 (67%)
First incidence (days)	420	304	456
Poly-3 test	P=0.003	P=0.143	P=0.004
All Organs: Benign or Malignant Neoplasms			
Overall rate	35/50 (70%)	45/50 (90%)	50/50 (100%)
Adjusted rate	70.0%	91.6%	100.0%
Terminal rate	26/41 (63%)	33/37 (89%)	36/36 (100%)
First incidence (days)	420	304	401
Poly-3 test	P<0.001	P=0.005	P<0.001

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for kidney, liver, lung, and spleen; 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 C4a
Historical Incidence of Liver Neoplasms in Vehicle Control Male B6C3F$_1$ Mice[a]

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

[a] Data as of 12 July 2000. Vehicle controls from the sodium xylenesulfonate study were excluded because liver neoplasms were associated with hepatitis due to *Helicobacter hepaticus* infection.

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

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

[a] Data as of 12 July 2000

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	5	7	7
Natural deaths	4	6	7
Survivors			
Terminal sacrifice	41	37	36
Animals examined microscopically	50	50	50
Alimentary System			
Intestine small, duodenum	(49)	(50)	(50)
Ulcer		1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)
Inflammation		1 (2%)	
Lymphatic, hyperplasia		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)		
Basophilic focus		3 (6%)	
Clear cell focus	8 (16%)	8 (16%)	4 (8%)
Degeneration, cystic	1 (2%)		
Eosinophilic focus	20 (40%)	29 (58%)	31 (62%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)
Mixed cell focus	6 (12%)	7 (14%)	6 (12%)
Necrosis	1 (2%)	3 (6%)	2 (4%)
Bile duct, hyperplasia			1 (2%)
Mesentery	(3)	(3)	(4)
Artery, inflammation			1 (25%)
Fat, necrosis	1 (33%)	1 (33%)	2 (50%)
Pancreas	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	5 (10%)
Hypertrophy, focal			1 (2%)
Inflammation, granulomatous			1 (2%)
Duct, cyst		1 (2%)	1 (2%)
Duct, hyperplasia			1 (2%)
Salivary glands	(50)	(50)	(50)
Inflammation		1 (2%)	
Inflammation, granulomatous			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)	
Ulcer		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
Dysplasia		1 (2%)	
Erosion	1 (2%)		
Hyperplasia		1 (2%)	
Inflammation, granulomatous			1 (2%)
Tooth		(1)	
Inflammation		1 (100%)	

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Cardiovascular System			
Blood vessel	(50)	(50)	(50)
Aorta, inflammation	1 (2%)		
Heart	(50)	(50)	(50)
Degeneration		3 (6%)	
Artery, inflammation		1 (2%)	
Atrium, thrombosis			1 (2%)
Coronary artery, thrombosis		1 (2%)	
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Angiectasis		1 (2%)	
Hyperplasia	3 (6%)	6 (12%)	3 (6%)
Hypertrophy	28 (56%)	30 (60%)	26 (52%)
Necrosis		1 (2%)	
Capsule, hyperplasia	8 (16%)	15 (30%)	11 (22%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	
Isets, pancreatic	(50)	(50)	(50)
Hyperplasia	21 (12%)	23 (46%)	21 (42%)
Pituitary gland	(45)	(47)	(49)
Cyst	2 (4%)	3 (6%)	
Pars distalis, hyperplasia	4 (9%)	2 (4%)	4 (8%)
Pars intermedia, hyperplasia		1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
Follicular cell, hyperplasia	11 (22%)	20 (40%)	23 (46%)
General Body System			
None			
Genital System			
Epididymis	(50)	(50)	(50)
Granuloma sperm	2 (4%)	1 (2%)	2 (4%)
Penis			(1)
Congestion			1 (100%)
Preputial Gland	(49)	(50)	(50)
Cyst	21 (43%)	21 (42%)	14 (28%)
Inflammation	1 (2%)		1 (2%)
Prostate	(50)	(50)	(50)
Inflammation	1 (2%)		1 (2%)
Seminal vesicle	(50)	(49)	(50)
Inflammation, granulomatous			1 (2%)
Testes	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	1 (2%)
Mineralization			1 (2%)
Interstitial cell, hyperplasia			1 (2%)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hyperplasia	10 (20%)	10 (20%)	19 (38%)
Lymph node, mandibular	(47)	(45)	(44)
Hematopoietic cell proliferation		1 (2%)	
Lymph node, mesenteric	(46)	(48)	(47)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Atrophy			2 (4%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	3 (6%)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Inflammation, granulomatous			1 (2%)
Spleen	(50)	(50)	(50)
Angiectasis			1 (2%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	25 (50%)	23 (46%)	30 (60%)
Thymus	(43)	(44)	(41)
Atrophy	13 (30%)	13 (30%)	14 (34%)
Integumentary System			
Skin	(50)	(50)	(50)
Control, edema		1 (2%)	
Control, infiltration cellular, mast cell	1 (2%)		
Epidermis, skin, site of application, hyperplasia	5 (10%)	47 (94%)	50 (100%)
Lymphatic, angiectasis		1 (2%)	
Sebaceous gland, skin, site of application, hyperplasia		44 (88%)	49 (98%)
Skin, site of application, hyperkeratosis		24 (48%)	23 (46%)
Skin, site of application, inflammation	2 (4%)	2 (4%)	2 (4%)
Skin, site of application, parakeratosis	1 (2%)	4 (8%)	5 (10%)
Skin, site of application, ulcer	1 (2%)		7 (14%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Hyperostosis	1 (2%)		
Nervous System			
Brain	(50)	(50)	(50)
Neuron, necrosis		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Inflammation	1 (2%)		1 (2%)
Inflammation, granulomatous			1 (2%)
Pigmentation, hemosiderin		1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	4 (8%)	1 (2%)
Nose	(50)	(50)	(50)
Inflammation	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation	1 (2%)	1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Special Senses System			
Eye	(1)	(2)	(1)
Cornea, inflammation		2 (100%)	1 (100%)
Harderian gland	(3)	(3)	(6)
Hyperplasia	1 (33%)		1 (17%)
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet	1 (2%)	1 (2%)	
Cyst	12 (24%)	16 (32%)	11 (22%)
Inflammation, granulomatous			1 (2%)
Inflammation, suppurative			1 (2%)
Nephropathy	47 (94%)	49 (98%)	50 (100%)
Pigmentation, hemosiderin			3 (6%)
Artery, inflammation	2 (4%)		1 (2%)
Renal tubule, hyperplasia	1 (2%)		2 (4%)
Ureter	(1)		(1)
Inflammation, granulomatous			1 (100%)
Urinary bladder	(50)	(50)	(50)
Inflammation			1 (2%)
Inflammation, granulomatous			1 (2%)

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	11	11	15
Natural deaths	4	3	9
Survivors			
Died last week of study		1	
Terminal sacrifice	35	35	26
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(49)	(48)	(50)
Intestine large, rectum	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Polyp adenomatous		1 (2%)	
Intestine small, jejunum	(49)	(50)	(50)
Carcinoma		1 (2%)	
Leiomyosarcoma		1 (2%)	
Liver	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland		1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)		
Hemangiosarcoma, multiple	1 (2%)		
Hepatoblastoma		1 (2%)	2 (4%)
Hepatoblastoma, multiple			1 (2%)
Hepatocellular carcinoma	1 (2%)	17 (34%)	16 (32%)
Hepatocellular carcinoma, multiple	2 (4%)	4 (8%)	16 (32%)
Hepatocellular adenoma	8 (16%)	5 (10%)	5 (10%)
Hepatocellular adenoma, multiple	24 (48%)	39 (78%)	38 (76%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Mesentery	(12)	(9)	(8)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (11%)	
Pancreas	(50)	(50)	(50)
Hemangioma		1 (2%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Salivary glands	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)
Tongue			(1)
Squamous cell carcinoma			1 (100%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)		

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

	Vehicle Control	100 mg/kg	200 mg/kg
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Adenoma	1 (2%)		
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma malignant			1 (2%)
Pheochromocytoma complex			1 (2%)
Pheochromocytoma benign	2 (4%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)
Pituitary gland	(48)	(50)	(49)
Pars distalis, adenoma	5 (10%)	2 (4%)	1 (2%)
Pars distalis, carcinoma	1 (2%)	1 (2%)	
Pars intermedia, adenoma		1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma	2 (4%)	5 (10%)	3 (6%)
General Body System			
None			
Genital System			
Clitoral gland	(48)	(49)	(47)
Carcinoma		1 (2%)	
Histiocytic sarcoma		1 (2%)	
Ovary	(50)	(50)	(50)
Cystadenoma	3 (6%)		1 (2%)
Granulosa cell tumor malignant		1 (2%)	
Hemangioma		1 (2%)	
Hemangiosarcoma			1 (2%)
Histiocytic sarcoma		1 (2%)	
Luteoma	1 (2%)		
Teratoma benign			1 (2%)
Teratoma malignant			1 (2%)
Uterus	(50)	(50)	(50)
Hemangioma	1 (2%)		
Histiocytic sarcoma			1 (2%)
Leiomyosarcoma	1 (2%)		
Polyp stromal	1 (2%)	2 (4%)	2 (4%)
Vagina		(1)	
Histiocytic sarcoma		1 (100%)	
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, metastatic, ovary			1 (2%)
Histiocytic sarcoma		1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System (continued)			
Lymph node	(7)	(3)	(6)
Bronchial, histiocytic sarcoma		1 (33%)	
Inguinal, fibrosarcoma, metastatic, skin	1 (14%)		
Lumbar, histiocytic sarcoma			1 (17%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (17%)
Mediastinal, carcinoma, metastatic, thyroid gland	1 (14%)		
Mediastinal, hepatoblastoma, metastatic, liver		1 (33%)	
Mediastinal, histiocytic sarcoma		1 (33%)	1 (17%)
Pancreatic, carcinoma, metastatic, thyroid gland	1 (14%)		
Lymph node, mandibular	(49)	(47)	(49)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Lymph node, mesenteric	(48)	(50)	(49)
Histiocytic sarcoma		1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Spleen	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Thymus	(47)	(40)	(41)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)	
Integumentary System			
Mammary gland	(48)	(49)	(50)
Carcinoma	1 (2%)		1 (2%)
Skin	(50)	(50)	(50)
Melanoma benign			1 (2%)
Melanoma malignant			1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)	
Subcutaneous tissue, melanoma benign	1 (2%)	1 (2%)	
Subcutaneous tissue, control, sarcoma	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland		1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)	2 (4%)	
Carcinoma, metastatic, thyroid gland	1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	3 (6%)	9 (18%)
Histiocytic sarcoma		1 (2%)	1 (2%)
Mediastinum, leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Nose	(50)	(50)	(49)
Carcinoma, metastatic, harderian gland	1 (2%)	1 (2%)	
Special Senses System			
Eye	(1)	(2)	(1)
Carcinoma, metastatic, harderian gland		1 (50%)	
Harderian gland	(1)	(2)	(1)
Carcinoma	1 (100%)	2 (100%)	1 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver		1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)	
Renal tubule, adenoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Hemangioma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant	13 (26%)	5 (10%)	7 (14%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	47	48	50
Total primary neoplasms	78	104	110
Total animals with benign neoplasms	39	45	45
Total benign neoplasms	53	66	56
Total animals with malignant neoplasms	23	30	41
Total malignant neoplasms	25	38	54
Total animals with metastatic neoplasms	5	8	11
Total metastatic neoplasms	11	21	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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Coconut Oil Acid Diethanolamine Condensate: Vehicle Control

Number of Days on Study	429	479	506	568	589	617	664	679	681	687	701	702	713	719	726	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	187	186	189	158	190	200	174	173	196	159	193	180	155	165	183	151	152	153	154	161	162	164	166	168	169
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland					X																				
Hemangiosarcoma, multiple																			X						
Hepatocellular carcinoma												X													
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma				X				X					X					X							
Hepatocellular adenoma, multiple											X	X		X		X				X	X	X	X		X
Histiocytic sarcoma							X																		
Mesentery										+	+	+			+						+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X																X			X		
Pars distalis, carcinoma			X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma					X																				
Follicular cell, adenoma																							X		
General Body System																									
None																									

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

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	170	171	175	176	178	179	185	188	191	192	197	198	199	156	157	160	163	167	172	177	181	182	184	194	195	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma																										1
Hepatocellular carcinoma, multiple																X										2
Hepatocellular adenoma										X											X	X		X		8
Hepatocellular adenoma, multiple	X	X		X	X	X	X	X	X		X	X				X	X	X	X	X						24
Histiocytic sarcoma																										1
Mesentery				+		+						+							+		+			+	+	12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pars distalis, adenoma																X				X						5
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
Follicular cell, adenoma								X																		2
General Body System																										
None																										

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

Number of Days on Study	429	479	506	568	589	617	664	679	681	687	701	702	713	719	726	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	187	186	189	158	190	200	174	173	196	159	193	180	155	165	183	151	152	153	154	161	162	164	166	168	169
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma							X																			
Luteoma																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																										
Leiomyosarcoma								X																		
Polyp stromal							X																			
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+													+							
Inguinal, fibrosarcoma, metastatic, skin																										
Mediastinal, carcinoma, metastatic, thyroid gland					X																					
Pancreatic, carcinoma, metastatic, thyroid gland					X																					
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland					X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, melanoma benign																										
Subcutaneous tissue, control, sarcoma																	X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X									
Alveolar/bronchiolar adenoma, multiple																										
Carcinoma, metastatic, harderian gland	X																									
Carcinoma, metastatic, thyroid gland					X																					
Hepatocellular carcinoma, metastatic, liver									X			X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland	X																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730		
Carcass ID Number	170	171	175	176	178	179	185	188	191	192	197	198	199	156	157	160	163	167	172	177	181	182	184	194	195		Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cystadenoma		X																		X							3
Luteoma								X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangioma													X														1
Leiomyosarcoma																											1
Polyp stromal																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node												+		+									+	+			7
Inguinal, fibrosarcoma, metastatic, skin																								X			1
Mediastinal, carcinoma, metastatic, thyroid gland																											1
Pancreatic, carcinoma, metastatic, thyroid gland																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, metastatic, thyroid gland																											1
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+		47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Carcinoma										X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Subcutaneous tissue, fibrosarcoma																								X			1
Subcutaneous tissue, melanoma benign												X															1
Subcutaneous tissue, control, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																											1
Alveolar/bronchiolar adenoma, multiple																									X		1
Carcinoma, metastatic, harderian gland																											1
Carcinoma, metastatic, thyroid gland																											1
Hepatocellular carcinoma, metastatic, liver																											2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, harderian gland																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

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

Number of Days on Study	429	479	506	568	589	617	664	679	681	687	701	702	713	719	726	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	187	186	189	158	190	200	174	173	196	159	193	180	155	165	183	151	152	153	154	161	162	164	166	168	169
Special Senses System																									
Eye	+																								
Harderian gland	+																								
Carcinoma	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymphoma malignant					X	X					X			X	X				X						X

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	170	171	175	176	178	179	185	188	191	192	197	198	199	156	157	160	163	167	172	177	181	182	184	194	195	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																		X								1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant													X	X	X	X		X					X			13

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

Number of Days on Study	473	553	561	567	584	611	616	618	629	644	649	678	680	691	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	249	207	231	243	204	213	208	212	234	235	226	219	214	229	201	202	203	205	209	215	216	220	221	222	223
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leiomyosarcoma	X																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland				X																					
Hepatoblastoma									X																
Hepatocellular carcinoma					X			X	X								X				X				
Hepatocellular carcinoma, multiple													X										X		
Hepatocellular adenoma						X				X												X	X		
Hepatocellular adenoma, multiple			X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X			X	X
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Mesentery	+						+	+	+																
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars distalis, carcinoma							X																		
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X									X		X			X

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	224	225	227	228	230	240	244	245	246	248	250	206	210	211	217	218	232	233	236	237	238	239	241	242	247	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Polyp adenomatous					X																					1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Leiomyosarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Hepatoblastoma																										1
Hepatocellular carcinoma	X	X			X		X			X	X				X	X		X	X		X			X		17
Hepatocellular carcinoma, multiple				X		X																				4
Hepatocellular adenoma		X																								5
Hepatocellular adenoma, multiple	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	39
Histiocytic sarcoma								X																		1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Mesentery						+		+		+						+									+	9
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma							X																			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																				+						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign															X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X																						X	2
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma			X																							5

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

Number of Days on Study	473	553	561	567	584	611	616	618	629	644	649	678	680	691	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	249	207	231	243	204	213	208	212	234	235	226	219	214	229	201	202	203	205	209	215	216	220	221	222	223
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																						
Histiocytic sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Hemangioma																									
Histiocytic sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X							X						
Vagina																									
Histiocytic sarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node									+	+															
Bronchial, histiocytic sarcoma																									
Mediastinal, hepatoblastoma, metastatic, liver									X																
Mediastinal, histiocytic sarcoma																									
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Thymus	+	+	+	+	+	M	+	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma													X												
Subcutaneous tissue, melanoma benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland							X																		
Peripheral nerve								+																	
Spinal cord								+																	

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	224	225	227	228	230	240	244	245	246	248	250	206	210	211	217	218	232	233	236	237	238	239	241	242	247	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Histiocytic sarcoma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant	X																									1
Hemangioma		X																								1
Histiocytic sarcoma								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										2
Vagina																			+							1
Histiocytic sarcoma																			X							1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Lymph node								+																		3
Bronchial, histiocytic sarcoma								X																		1
Mediastinal, hepatoblastoma, metastatic, liver																										1
Mediastinal, histiocytic sarcoma								X																		1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma								X																		1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Thymus	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	40
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, melanoma benign				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve																										1
Spinal cord																										1

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

Number of Days on Study	473	553	561	567	584	611	616	618	629	644	649	678	680	691	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	249	207	231	243	204	213	208	212	234	235	226	219	214	229	201	202	203	205	209	215	216	220	221	222	223
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland				X											X										
Hepatoblastoma, metastatic, liver									X																
Hepatocellular carcinoma, metastatic, liver																							X		
Histiocytic sarcoma																									
Mediastinum, leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+											+										
Carcinoma, metastatic, harderian gland				X																					
Harderian gland				+											+										
Carcinoma				X											X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver									X																
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, intestine small, jejunum	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant					X		X			X				X											

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	224	225	227	228	230	240	244	245	246	248	250	206	210	211	217	218	232	233	236	237	238	239	241	242	247	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X			X										3
Alveolar/bronchiolar adenoma, multiple																						X				1
Alveolar/bronchiolar carcinoma																									X	1
Carcinoma, metastatic, harderian gland																										2
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver						X												X								3
Histiocytic sarcoma								X																		1
Mediastinum, leiomyosarcoma, metastatic, intestine small, jejunum																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Carcinoma, metastatic, harderian gland																										1
Harderian gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma								X																		1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X											X							2
Lymphoma malignant																X										5

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

Number of Days on Study	098	366	422	506	552	564	567	580	610	610	621	630	632	649	653	653	661	665	672	701	702	711	722	728	729
Carcass ID Number	251	255	260	297	252	258	271	270	262	293	287	259	286	283	278	298	264	266	267	300	280	290	276	272	253
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma							X																	X	
Hepatoblastoma, multiple																									
Hepatocellular carcinoma		X		X							X		X	X	X	X								X	
Hepatocellular carcinoma, multiple					X				X								X		X		X		X		X
Hepatocellular adenoma		X	X																X					X	
Hepatocellular adenoma, multiple					X		X	X	X	X	X	X	X	X	X		X	X		X		X			X
Histiocytic sarcoma																X									
Mesentery						+											+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+													
Squamous cell carcinoma												X													
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	254	256	257	261	263	268	269	277	279	281	282	285	289	291	294	295	299	265	273	274	275	284	288	292	296	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																										2
Hepatoblastoma, multiple																				X						1
Hepatocellular carcinoma	X		X	X				X	X		X	X				X										16
Hepatocellular carcinoma, multiple													X	X	X		X			X	X	X		X	X	16
Hepatocellular adenoma																									X	5
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	38
Histiocytic sarcoma																										1
Mesentery										+	+		+							+		+	+			8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																	X									1
Pheochromocytoma complex																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma											X															1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X	X												X							3
General Body System																										
None																										

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

Number of Days on Study	098	366	422	506	552	564	567	580	610	610	621	630	632	649	653	653	661	665	672	701	702	711	722	728	729
Carcass ID Number	251	255	260	297	252	258	271	270	262	293	287	259	286	283	278	298	264	266	267	300	280	290	276	272	253
Genital System																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangiosarcoma										X															
Teratoma benign			X																						
Teratoma malignant	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, ovary										X															
Lymph node				+		+									+	+						+			
Lumbar, histiocytic sarcoma																X									
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Mediastinal, histiocytic sarcoma																X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma																X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	M	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma benign																									
Melanoma malignant																					X				
Subcutaneous tissue, fibrosarcoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																							
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma				X																					
Hepatoblastoma, metastatic, liver							X																		
Hepatocellular carcinoma, metastatic, liver				X													X		X		X				X
Histiocytic sarcoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	254	256	257	261	263	268	269	277	279	281	282	285	289	291	294	295	299	265	273	274	275	284	288	292	296	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																				X						1
Hemangiosarcoma																										1
Teratoma benign																										1
Teratoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal									X	X																2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Hemangiosarcoma, metastatic, ovary																										1
Lymph node																						+				6
Lumbar, histiocytic sarcoma																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																					X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Melanoma benign													X													1
Melanoma malignant																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic liver												X	X				X			X						9
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	098	366	422	506	552	564	567	580	610	610	621	630	632	649	653	653	661	665	672	701	702	711	722	728	729
Carcass ID Number	251	255	260	297	252	258	271	270	262	293	287	259	286	283	278	298	264	266	267	300	280	290	276	272	253
Special Senses System																									
Eye																									
Harderian gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Renal tubule, adenoma											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant						X									X							X			

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	
Carcass ID Number	254	256	257	261	263	268	269	277	279	281	282	285	289	291	294	295	299	265	273	274	275	284	288	292	296	Total Tissues/ Tumors
Special Senses System																										
Eye																	+									1
Harderian gland																	+									1
Carcinoma																	X									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant						X											X		X			X				7

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

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatocellular Adenoma			
Overall rate[a]	32/50 (64%)	44/50 (88%)	43/50 (86%)
Adjusted rate[b]	69.0%	90.3%	90.7%
Terminal rate[c]	26/35 (74%)	32/36 (89%)	25/26 (96%)
First incidence (days)	568	561	366
Poly-3 test[d]	P=0.002	P=0.006	P=0.005
Liver: Hepatocellular Carcinoma			
Overall rate	3/50 (6%)	21/50 (42%)	32/50 (64%)
Adjusted rate	6.6%	45.8%	70.4%
Terminal rate	1/35 (3%)	17/36 (47%)	18/26 (69%)
First incidence (days)	681	584	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	33/50 (66%)	46/50 (92%)	48/50 (96%)
Adjusted rate	70.9%	94.4%	99.0%
Terminal rate	26/35 (74%)	34/36 (94%)	26/26 (100%)
First incidence (days)	568	561	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Liver: Hepatoblastoma			
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.2%	7.3%
Terminal rate	0/35 (0%)	0/36 (0%)	1/26 (4%)
First incidence (days)	—[e]	629	567
Poly-3 test	P=0.054	P=0.498	P=0.103
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	3/50 (6%)	21/50 (42%)	33/50 (66%)
Adjusted rate	6.6%	45.8%	71.8%
Terminal rate	1/35 (3%)	17/36 (47%)	18/26 (69%)
First incidence (days)	681	584	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	33/50 (66%)	46/50 (92%)	48/50 (96%)
Adjusted rate	70.9%	94.4%	99.0%
Terminal rate	26/35 (74%)	34/36 (94%)	26/26 (100%)
First incidence (days)	568	561	366
Poly-3 test	P<0.001	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	4.4%	9.0%	0.0%
Terminal rate	2/35 (6%)	3/36 (8%)	0/26 (0%)
First incidence (days)	729 (T)	691	—
Poly-3 test	P=0.277N	P=0.330	P=0.262N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted rate	4.4%	11.2%	2.4%
Terminal rate	2/35 (6%)	4/36 (11%)	0/26 (0%)
First incidence (days)	729 (T)	691	506
Poly-3 test	P=0.477N	P=0.209	P=0.531N
Ovary: Cystadenoma			
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.6%	0.0%	2.5%
Terminal rate	2/35 (6%)	0/36 (0%)	1/26 (4%)
First incidence (days)	664	—	729 (T)
Poly-3 test	P=0.191N	P=0.123N	P=0.346N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	5/48 (10%)	2/50 (4%)	1/49 (2%)
Adjusted rate	11.3%	4.5%	2.5%
Terminal rate	4/34 (12%)	2/36 (6%)	1/26 (4%)
First incidence (days)	568	729 (T)	729 (T)
Poly-3 test	P=0.073N	P=0.214N	P=0.128N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	6/48 (13%)	3/50 (6%)	1/49 (2%)
Adjusted rate	13.4%	6.7%	2.5%
Terminal rate	4/34 (12%)	2/36 (6%)	1/26 (4%)
First incidence (days)	506	616	729 (T)
Poly-3 test	P=0.048N	P=0.242N	P=0.078N
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rate	4.4%	11.2%	7.4%
Terminal rate	2/35 (6%)	4/36 (11%)	3/26 (12%)
First incidence (days)	729 (T)	649	729 (T)
Poly-3 test	P=0.357	P=0.211	P=0.451
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.6%	4.5%	4.9%
Terminal rate	3/35 (9%)	2/36 (6%)	1/26 (4%)
First incidence (days)	729 (T)	729 (T)	610
Poly-3 test	P=0.449N	P=0.509N	P=0.544N
All Organs: Malignant Lymphoma			
Overall rate	13/50 (26%)	5/50 (10%)	7/50 (14%)
Adjusted rate	28.1%	10.9%	16.8%
Terminal rate	8/35 (23%)	1/36 (3%)	4/26 (15%)
First incidence (days)	589	584	564
Poly-3 test	P=0.094N	P=0.033N	P=0.158N

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

	Vehicle Control	100 mg/kg	200 mg/kg
All Organs: Benign Neoplasms			
Overall rate	39/50 (78%)	45/50 (90%)	45/50 (90%)
Adjusted rate	83.1%	92.4%	94.9%
Terminal rate	30/35 (86%)	33/36 (92%)	26/26 (100%)
First incidence (days)	568	561	366
Poly-3 test	P=0.029	P=0.126	P=0.048
All Organs: Malignant Neoplasms			
Overall rate	23/50 (46%)	30/50 (60%)	41/50 (82%)
Adjusted rate	47.4%	61.8%	84.6%
Terminal rate	12/35 (34%)	20/36 (56%)	20/26 (77%)
First incidence (days)	429	473	98
Poly-3 test	P<0.001	P=0.109	P<0.001
All Organs: Benign or Malignant Neoplasms			
Overall rate	47/50 (94%)	48/50 (96%)	50/50 (100%)
Adjusted rate	95.4%	97.1%	100.0%
Terminal rate	33/35 (94%)	35/36 (97%)	26/26 (100%)
First incidence (days)	429	473	98
Poly-3 test	P=0.109	P=0.533	P=0.180

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and 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 D4
Historical Incidence of Liver Neoplasms in Vehicle Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratories				
Benzethonium Chloride	20/52	12/52	0/52	27/52
Coconut Oil Acid Diethanolamine Condensate	32/50	3/50	0/50	33/50
Diethanolamine	32/50	5/50	0/50	33/50
Lauric Acid Diethanolamine Condensate	23/50	10/50	0/50	28/50
Oleic Acid Diethanolamine Condensate	26/50	5/50	1/50	28/50
Overall Historical Incidence				
Total	133/252 (52.8%)	35/252 (13.9%)	1/252 (0.4%)	149/252 (59.1%)
Mean ± standard deviation	52.8% ± 11.4%	13.9% ± 7.3%	0.4% ± 0.9%	59.1% ± 6.4%
Range	38%-64%	6%-23%	0%-2%	52%-66%

[a] Data as of 12 July 2000. 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 Coconut Oil Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	11	11	15
Natural deaths	4	3	9
Survivors			
Died last week of study		1	
Terminal sacrifice	35	35	26
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Inflammation		1 (2%)	
Intestine large, rectum	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)
Erosion			2 (4%)
Ulcer		1 (2%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Inflammation			1 (2%)
Ulcer	1 (2%)		
Mucosa, hyperplasia		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	
Basophilic focus	2 (4%)		
Clear cell focus	2 (4%)	2 (4%)	2 (4%)
Eosinophilic focus	18 (36%)	25 (50%)	24 (48%)
Fibrosis	2 (4%)	1 (2%)	
Inflammation, suppurative		1 (2%)	
Mixed cell focus	1 (2%)	5 (10%)	
Necrosis	2 (4%)	5 (10%)	8 (16%)
Bile duct, hyperplasia	1 (2%)	1 (2%)	
Mesentery	(12)	(9)	(8)
Fat, inflammation	2 (17%)		
Fat, necrosis	9 (75%)	8 (89%)	7 (88%)
Pancreas	(50)	(50)	(50)
Atrophy	1 (2%)	4 (8%)	1 (2%)
Hypertrophy			1 (2%)
Hypertrophy, focal	3 (6%)	1 (2%)	1 (2%)
Duct, cyst	2 (4%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Erosion		1 (2%)	1 (2%)
Hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)
Inflammation		1 (2%)	
Ulcer		1 (2%)	
Stomach, glandular	(50)	(50)	(50)
Erosion	1 (2%)		2 (4%)
Inflammation	2 (4%)		
Mineralization	2 (4%)	1 (2%)	1 (2%)
Ulcer	1 (2%)		
Tooth		(1)	
Inflammation		1 (100%)	

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

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

	Vehicle Control	100 mg/kg	200 mg/kg
Cardiovascular System			
Heart	(50)	(50)	(50)
Infiltration cellular, mononuclear cell		1 (2%)	
Mineralization	1 (2%)	1 (2%)	1 (2%)
Artery, inflammation	1 (2%)		
Endocrine System			
Adrenal cortex	(50)	(50)	(50)
Hematopoietic cell proliferation		1 (2%)	
Hyperplasia		1 (2%)	1 (2%)
Hypertrophy	1 (2%)		
Vacuolization cytoplasmic	1 (2%)		
Capsule, hyperplasia		2 (4%)	
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	1 (2%)		2 (4%)
Parathyroid gland	(37)	(42)	(43)
Cyst	1 (3%)		
Hyperplasia, focal		1 (2%)	
Pituitary gland	(48)	(50)	(49)
Angiectasis	1 (2%)		
Pars distalis, hyperplasia	28 (58%)	31 (62%)	27 (55%)
Pars intermedia, hyperplasia		1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)
Follicular cell, hyperplasia	27 (54%)	36 (72%)	33 (66%)
General Body System			
None			
Genital System			
Clitoral gland	(48)	(49)	(47)
Inflammation	1 (2%)		
Ovary	(50)	(50)	(50)
Angiectasis		2 (4%)	
Cyst	15 (30%)	14 (28%)	15 (30%)
Hemorrhage	2 (4%)		2 (4%)
Mineralization	1 (2%)		
Granulosa cell, hyperplasia		1 (2%)	1 (2%)
Uterus	(50)	(50)	(50)
Decidual reaction	1 (2%)		
Hyperplasia	37 (74%)	26 (52%)	22 (44%)
Inflammation, suppurative		1 (2%)	
Thrombosis	1 (2%)	1 (2%)	

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hyperplasia	7 (14%)	10 (20%)	19 (38%)
Myelofibrosis	21 (42%)	21 (42%)	19 (38%)
Lymph node	(7)	(3)	(6)
Inguinal, hematopoietic cell proliferation			1 (17%)
Mediastinal, hematopoietic cell proliferation			1 (17%)
Renal, hematopoietic cell proliferation			1 (17%)
Lymph node, mandibular	(49)	(47)	(49)
Hematopoietic cell proliferation			2 (4%)
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, plasma cell			1 (2%)
Lymph node, mesenteric	(48)	(50)	(49)
Angiectasis		1 (2%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)		
Hyperplasia, plasma cell		1 (2%)	
Inflammation			1 (2%)
Spleen	(50)	(50)	(50)
Accessory spleen		1 (2%)	
Hematopoietic cell proliferation	33 (66%)	33 (66%)	36 (72%)
Lymphoid follicle, hyperplasia	1 (2%)	5 (10%)	
Thymus	(47)	(40)	(41)
Atrophy	7 (15%)	4 (10%)	8 (20%)
Hyperplasia, lymphoid	1 (2%)	2 (5%)	1 (2%)
Integumentary System			
Skin	(50)	(50)	(50)
Control, edema	1 (2%)		
Control, hyperkeratosis	1 (2%)		
Control, inflammation			3 (6%)
Control, parakeratosis	1 (2%)		
Epidermis, control, hyperplasia	1 (2%)		
Epidermis, skin, site of application, hyperplasia	9 (18%)	47 (94%)	50 (100%)
Sebaceous gland, skin, site of application, hyperplasia		42 (84%)	48 (96%)
Skin, site of application, hyperkeratosis	5 (10%)	30 (60%)	40 (80%)
Skin, site of application, inflammation	3 (6%)	2 (4%)	11 (22%)
Skin, site of application, parakeratosis	3 (6%)	4 (8%)	16 (32%)
Skin, site of application, ulcer	1 (2%)		3 (6%)
Subcutaneous tissue, control, hemorrhage			1 (2%)
Musculoskeletal System			
Bone	(50)	(50)	(50)
Osteomalacia		1 (2%)	
Joint, inflammation, chronic		1 (2%)	
Nervous System			
Brain	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)	
Neuron, necrosis		2 (4%)	3 (6%)

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

	Vehicle Control	100 mg/kg	200 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Inflammation		2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	2 (4%)
Nose	(50)	(50)	(49)
Inflammation		1 (2%)	2 (4%)
Nasolacrimal duct, inflammation		1 (2%)	
Special Senses System			
Eye	(1)	(2)	(1)
Degeneration		1 (50%)	
Cornea, inflammation	1 (100%)		1 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Accumulation, hyaline droplet	2 (4%)		1 (2%)
Cyst			1 (2%)
Hydronephrosis	1 (2%)	1 (2%)	1 (2%)
Mineralization	2 (4%)		
Nephropathy	27 (54%)	24 (48%)	15 (30%)
Pigmentation, hemosiderin	1 (2%)		2 (4%)
Pigmentation, hemoglobin		1 (2%)	
Glomerulus, thrombosis			1 (2%)
Renal tubule, degeneration		1 (2%)	
Renal tubule, hyperplasia		2 (4%)	1 (2%)
Urinary bladder	(50)	(50)	(50)
Inflammation	1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1988). Coconut oil 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 coconut oil 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). Coconut oil acid diethanolamine condensate was supplied as a coded aliquot by Radian Corporation. The high dose of coconut oil 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 coconut oil acid diethanolamine condensate continued for 4 hours, at which time the medium plus coconut oil 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 had to be significant ($P \leq 0.05$) for coconut oil acid diethanolamine condensate to be considered positive, i.e., capable of inducing TFT resistance. A single significant

response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Coconut oil 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 coconut oil 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 coconut oil acid diethanolamine condensate in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing coconut oil 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 coconut oil 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 coconut oil 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 coconut oil acid diethanolamine condensate for 10 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 coconut oil acid diethanolamine condensate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 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 ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.,* (1990). At the end of 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 dose 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. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

Results of *in vitro* assays for genotoxicity with coconut oil acid diethanolamine condensate were uniformly negative. It did not induce mutations in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation (Zeiger *et al.*, 1988; Table E1). The highest concentration was limited to 200 μg/plate by toxicity. No increase in mutant L5178Y mouse lymphoma cell colonies was observed after exposure to coconut oil acid diethanolamine condensate, with or without S9 (Table E2). A single positive response noted at 8 nL/mL in the second trial conducted without S9 was not reproducible, and the test results overall were considered to be negative. In tests for induction of chromosomal damage, no increases in the frequencies of SCEs (Table E3) or Abs (Table E4) were observed in cultured CHO cells after incubation with coconut oil acid diethanolamine condensate, with or without S9.

In contrast to the negative results obtained in *in vitro* assays, positive results were obtained in a 14-week dermal study conducted with coconut oil acid diethanolamine condensate in male and female mice. At the end of 14 weeks, significant increases in the frequencies of micronucleated NCEs were seen in peripheral blood of both male and female mice (Table E5). Statistical analysis of the data showed positive trends for both data sets as well as significantly elevated micronucleus frequencies at the highest dose tested (800 mg/kg) in male and female mice.

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

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0.0	118 ± 4.3	171 ± 7.2	101 ± 2.9	145 ± 9.2	103 ± 4.1	168 ± 10.5
	0.1	101 ± 1.5	170 ± 8.5				
	0.3	111 ± 3.8	144 ± 12.2				
	1.0	91 ± 5.0	131 ± 6.8				
	3.3	97 ± 5.8	125 ± 5.2	87 ± 3.1	160 ± 2.5	86 ± 7.5	163 ± 17.9
	6.7	91 ± 3.0	133 ± 3.5				
	10.0			85 ± 5.8	152 ± 5.5	90 ± 4.6	151 ± 11.8
	33.0			88 ± 10.8	163 ± 3.2	86 ± 7.8	162 ± 6.6
	100.0			68 ± 3.5	172 ± 5.7	82 ± 3.7	166 ± 2.5
	200.0			41 ± 3.9[c]	130 ± 3.8	22 ± 5.2[c]	128 ± 6.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,302 ± 33.1	314 ± 8.2	1,286 ± 23.1	372 ± 10.2	2,232 ± 41.5	564 ± 29.3
TA1535	0.0	31 ± 4.4	46 ± 6.2	13 ± 1.5	34 ± 1.2	14 ± 1.8	40 ± 2.8
	0.1	31 ± 0.6	51 ± 2.3				
	0.3	25 ± 1.0	47 ± 5.2				
	1.0	32 ± 2.1	39 ± 2.9				
	3.3	28 ± 3.7	43 ± 2.8	11 ± 3.2	34 ± 4.2	13 ± 2.6	31 ± 3.8
	6.7	25 ± 1.5[c]	37 ± 3.5				
	10.0			10 ± 3.0	40 ± 3.8	8 ± 1.3	35 ± 2.0
	33.0			9 ± 1.0	35 ± 3.2	9 ± 1.9	42 ± 2.1
	100.0			9 ± 1.5	39 ± 0.9	9 ± 1.5	36 ± 2.8
	200.0			8 ± 0.7	33 ± 3.7	4 ± 0.9	29 ± 5.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		876 ± 38.5	123 ± 9.8	82 ± 4.6	102 ± 5.0	104 ± 8.3	116 ± 9.4

TABLE E1
Mutagenicity of Coconut Oil Acid Diethanolamine Condensate in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA97	0.0	104 ± 4.4	81 ± 1.5	103 ± 9.0	217 ± 17.7	108 ± 3.0	72 ± 4.9	219 ± 6.8
	0.1	100 ± 1.7	90 ± 0.9					
	0.3	115 ± 9.2	90 ± 2.5					
	1.0	114 ± 0.7	91 ± 8.0					
	3.3	115 ± 11.5	100 ± 6.8	104 ± 3.2	194 ± 5.9	101 ± 1.5	81 ± 2.3	201 ± 8.7
	6.7	112 ± 7.9	73 ± 7.5					
	10.0			99 ± 8.4	174 ± 1.7	108 ± 3.8	72 ± 14.2	216 ± 9.1
	33.0			98 ± 2.9	204 ± 8.8	101 ± 12.9	68 ± 1.3	255 ± 2.3
	100.0			87 ± 5.4[c]	214 ± 2.3	104 ± 9.0	24 ± 5.4	225 ± 10.7
	200.0			2 ± 0.7[c]	231 ± 17.3	115 ± 4.3	3 ± 0.3	172 ± 2.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		909 ± 27.3	181 ± 7.5	768 ± 19.1	277 ± 6.2	238 ± 11.9	1,156 ± 15.3	460 ± 9.2
TA98	0.0	22 ± 2.6	31 ± 2.6	37 ± 2.9	43 ± 1.2		33 ± 1.8	36 ± 1.2
	0.1	18 ± 2.3	27 ± 1.9					
	0.3	16 ± 1.9	21 ± 0.3					
	1.0	16 ± 4.5	23 ± 3.2					
	3.3	18 ± 5.0	26 ± 3.3	37 ± 2.3	38 ± 3.8		36 ± 4.1	40 ± 1.2
	6.7	21 ± 4.4	20 ± 2.4					
	10.0			30 ± 2.0	39 ± 3.5		32 ± 1.8	40 ± 5.8
	33.0			29 ± 2.0	43 ± 1.9		26 ± 2.7	36 ± 3.2
	100.0			37 ± 5.3	43 ± 2.7		30 ± 1.0	43 ± 4.4
	200.0			31 ± 6.0	49 ± 6.8		32 ± 2.8	44 ± 3.3
Trial summary		Negative	Negative	Negative	Negative		Negative	Negative
Positive control		1,981 ± 74.7	171 ± 12.0	777 ± 21.0	103 ± 8.0		1,159 ± 50.0	194 ± 9.6

[a] Study was performed at Microbiological Associates, Inc. The detailed protocol and these data are presented by Zeiger *et al*. (1988). 0.0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Coconut Oil Acid Diethanolamine Condensate[a]

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Ethanol[c] (nL/mL)		72	81	134	62	
Methyl methanesulfonate[d] (μg/mL)						
	5	33	38	644	654	
		60	60	704	390	
		49	39	769	525	523*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	74	94	103	47	
		76	101	108	47	
		64	123	83	44	50
	1.25	83	90	118	47	
		63	67	95	50	49
		Lethal				
	2.5	53	65	72	46	
		77	77	114	49	
		75	74	128	57	50
	5	61	63	81	44	
		57	47	97	57	
		70	54	114	55	52
	6	69	53	126	61	
		64	46	99	52	
		70	46	89	42	52
	10	61	84	113	62	
		54	9	135	84	
		72	15	139	65	70
	12	Lethal				
		Lethal				
		Lethal				

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9 (continued)						
Trial 2						
Ethanol (nL/mL)		93	94	45	16	
Methyl methanesulfonate (μg/mL)						
	5	119	101	271	76	
		90	72	213	79	
		89	77	182	68	74*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	92	91	62	22	
		115	110	60	17	
		108	106	38	12	17
	4	91	90	48	18	
		96	113	42	15	
		100	99	61	20	18
	5	85	87	49	19	
		101	89	52	17	
		75	69	47	21	19
	6	91	76	72	26	
		90	99	53	20	
		93	82	44	16	21
	8	74	63	82	37	
		78	65	61	26	
		86	73	54	21	28*
	10	92	50	82	30	
		114	64	70	21	
		100	58	74	25	25
	12	75	50	65	29	
		99	27	54	18	
		77	45	68	30	26

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9 (continued)						
Trial 3						
Ethanol (nL/mL)		92	66	119	43	
Methyl methanesulfonate (μg/mL)						
	5	51	33	868	564	
		43	27	574	445	
		93	52	698	252	420*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	115	74	91	26	
		111	125	73	22	
		114	135	85	25	29
	1.5	102	113	77	25	
		116	200	87	25	
		103	135	93	30	27
	3	87	113	108	41	
		98	114	96	33	
		114	126	99	29	34
	6	112	92	86	26	
		83	84	110	44	
		92	83	104	38	36
	8	115	37	116	34	
		108	45	178	55	
		111	34	83	25	38
	10	101	25	85	28	
		107	76	109	34	
		94	20	87	31	31
	12	90	15	115	43	
		103	36	114	37	40
		Lethal				
	15	Lethal				
		Lethal				

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Ethanol (nL/mL)		84	76	138	55	
Methyl cholanthrene[d] (μg/mL)						
	2.5	66	57	781	392	
		60	68	680	377	
		80	45	822	344	371*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	83	93	136	54	
		71	102	179	84	
		102	129	111	36	57
	1.25	58	73	137	79	
		73	89	148	68	
		50	97	116	77	75
	2.5	78	117	134	57	
		74	117	138	62	
		83	105	141	56	59
	5	91	135	61	22	
		69	107	92	45	33
		Lethal				
	10	54	14	126	78	
		92	27	121	44	61
	15	Lethal				
		Lethal				
		Lethal				

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 2						
Ethanol (nL/mL)		78	117	119	51	
Methyl cholanthrene (μg/mL)						
	2.5	45	18	613	456	
		39	15	626	542	
		51	26	570	376	458*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	91	106	183	67	
		85	78	144	56	
		82	99	141	58	58
	4	88	137	184	70	
		95	121	215	75	
		103	144	206	67	71
	5	75	143	157	70	
		76	123	166	73	
		80	140	141	59	67
	6	72	113	181	84	
		67	73	141	70	
		83	131	170	69	74
	8	76	92	186	82	
		96	89	215	75	
		108	118	182	56	71
	10	105	81	194	62	
		83	81	202	81	
		75	79	137	61	68
	12	93	83	166	60	
		81	88	147	60	
		78	65	189	81	67

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 3						
Ethanol (nL/mL)		104	140	116	37	
Methyl cholanthrene (μg/mL)						
	2.5	100	76	578	194	
		105	69	605	192	
		90	73	457	169	185*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	88	98	113	43	
		103	48	60	19	
		98	114	102	35	34
	6	105	116	127	40	
		95	109	155	55	
		73	85	106	48	48
	8	71	84	101	48	
		96	115	143	50	
		107	111	101	32	43
	10	95	85	117	41	
		98	88	99	34	
		105	127	123	39	38
	12	102	105	121	40	
		105	85	97	31	
		90	117	98	36	36
	15	87	45	101	39	
		97	63	108	37	
		91	47	137	50	42
	20	107	135	97	30	
		93	131	118	42	
		104	92	110	35	36

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

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 4						
Ethanol (nL/mL)		82	145	147	60	
Methyl cholanthrene (μg/mL)						
	2.5	60	44	442	246	
		60	25	598	330	
		84	69	447	177	251*
Coconut oil acid diethanolamine condensate (nL/mL)						
	0	71	32	146	68	
		78	126	129	55	
		77	96	101	44	57
	5	66	113	113	57	
		67	78	86	43	
		65	89	93	48	49
	10	79	100	153	65	
		72	88	150	70	
		62	94	137	74	69
	15	66	100	100	51	
		79	103	147	62	
		66	108	115	58	57
	20	67	76	117	58	
		58	74	114	66	
		58	89	115	66	63
	30	57	78	93	55	
		72	95	122	57	
		53	38	91	57	56
	40	62	18	128	69	
		63	17	136	72	70
		Lethal				
	50	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 (MF) (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10^6 cells treated).
[c] Solvent control
[d] Positive control

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

Compound	Concentration (μg/mL)	Total Cells Scored	Total Chromosomes	Total SCEs	SCEs/Chromosome	SCEs/Cell	Hrs in BrdU	Relative Change of SCEs/Chromosome[b] (%)
-S9								
Summary: Negative								
Solvent control		50	1,048	397	0.37	7.9	26.0	
Mitomycin-C[c]	0.0005	50	1,048	557	0.53	11.1	26.0	40.30
	0.0050	10	210	231	1.10	23.1	26.0	190.38
Coconut oil acid diethanolamine condensate								
	0.5	50	1,050	341	0.32	6.8	26.0	–14.27
	1.6	50	1,050	392	0.37	7.8	26.0	–1.45
	5.0	50	1,049	393	0.37	7.9	26.0	–1.10
	16.0	50	1,048	375	0.35	7.5	26.0	–5.54
					P=0.446[d]			
+S9								
Trial 1								
Summary: Weakly positive								
Solvent control		50	1,053	355	0.33	7.1	26.0	
Cyclophosphamide[c]	0.1	50	1,049	522	0.49	10.4	26.0	47.60
	0.6	10	210	269	1.28	26.9	26.0	279.96
Coconut oil acid diethanolamine condensate								
	0.5	50	1,048	407	0.38	8.1	26.0	15.19
	5.0	50	1,049	435	0.41	8.7	26.0	23.00*
	16.0	50	1,045	408	0.39	8.2	26.0	15.81
					P=0.010			
Trial 2								
Summary: Negative								
Solvent control		50	1,048	455	0.43	9.1	26.0	
Cyclophosphamide	0.1	50	1,050	569	0.54	11.4	26.0	24.82
	0.6	10	209	212	1.01	21.2	26.0	133.64
Coconut oil acid diethanolamine condensate								
	5	50	1,050	423	0.40	8.5	26.0	–7.21
	10	50	1,049	473	0.45	9.5	26.0	3.86
	16	50	1,049	373	0.35	7.5	26.0	–18.10
	30	50	1,050	359	0.34	7.2	26.0	–21.25
					P=1.000			

* Positive response (P≥20% increase over solvent control)
[a] Study was performed at Environmental Health Research and Testing. The detailed protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] 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 Coconut Oil Acid Diethanolamine Condensate[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/Cell	Cells with Aberrations (%)
-S9					
Harvest time: 12 hours					
Summary: Negative					
Solvent control		200	2	0.01	1.0
Mitomycin-C[b]	0.0625	200	35	0.18	16.5
	0.2500	50	26	0.52	32.0
Coconut oil acid diethanolamine condensate					
	16	200	3	0.02	1.5
	30	200	3	0.02	1.5
	50	200	5	0.03	2.5
					P=0.134[c]
+S9					
Harvest time: 13 hours					
Summary: Negative					
Solvent control		200	2	0.01	1.0
Cyclophosphamide[b]	2.5	200	39	0.20	17.5
	7.5	50	24	0.48	38.0
Coconut oil acid diethanolamine condensate					
	16	200	5	0.03	2.5
	30	200	4	0.02	2.0
	50	200	4	0.02	2.0
					P=0.280

[a] Study was performed at Environmental Health Research and Testing. The detailed protocol is presented by Galloway *et al*. (1987).
[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 Mouse Peripheral Blood Erythrocytes Following Dermal Application of Coconut Oil Acid Diethanolamine Condensate for 14 Weeks[a]

Compound	Dose (mg/kg)	Number of Mice	Micronucleated NCEs/1,000 NCEs[b]
Male			
Ethanol[c]		5	1.60 ± 0.40
Coconut oil acid diethanolamine condensate			
	50	5	2.30 ± 0.25
	100	5	2.90 ± 0.43
	200	5	3.00 ± 0.61
	400	5	2.70 ± 0.20
	800	5	3.50 ± 0.42*
			P=0.015[d]
Female			
Ethanol[c]		5	1.40 ± 0.10
Coconut oil acid diethanolamine condensate			
	50	5	1.70 ± 0.25
	100	5	2.20 ± 0.25
	200	5	2.30 ± 0.41
	400	5	2.10 ± 0.37
	800	5	3.40 ± 0.19*
			P=0.001

* Significantly different from vehicle control (P≤0.005)
[a] Study was performed at Environmental Health Research and Testing, Inc. 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 Coconut Oil Acid Diethanolamine Condensate** **196**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Coconut Oil 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	10	8	7	10	9	9
Day 24	10	10	9	7	10	10
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 4	46.2 ± 0.6	44.1 ± 0.5	43.4 ± 0.5**	44.7 ± 0.5	45.6 ± 0.8	44.2 ± 0.5
Day 24	51.1 ± 0.8	50.0 ± 0.6	49.5 ± 0.7	50.3 ± 0.7	49.8 ± 0.8	48.0 ± 0.8**
Week 14	47.5 ± 0.5	49.2 ± 0.4	48.4 ± 0.4	49.5 ± 0.5	46.7 ± 0.4	44.8 ± 0.5*
Hemoglobin (g/dL)						
Day 4	16.1 ± 0.2	15.4 ± 0.2	15.2 ± 0.1*	15.4 ± 0.1	15.9 ± 0.2	15.5 ± 0.2
Day 24	17.5 ± 0.2	17.4 ± 0.1	17.2 ± 0.2	17.3 ± 0.2	17.4 ± 0.2	16.9 ± 0.2
Week 14	15.9 ± 0.1	16.5 ± 0.1	16.3 ± 0.1	16.5 ± 0.1	15.6 ± 0.1	14.9 ± 0.1*
Erythrocytes ($10^6/\mu L$)						
Day 4	7.41 ± 0.12	7.03 ± 0.10	6.99 ± 0.10	7.13 ± 0.08	7.33 ± 0.14	7.10 ± 0.07
Day 24	8.63 ± 0.14	8.51 ± 0.10	8.45 ± 0.13	8.57 ± 0.14	8.56 ± 0.12	8.24 ± 0.14
Week 14	8.61 ± 0.11	9.06 ± 0.07*	8.83 ± 0.08	9.19 ± 0.10**	8.76 ± 0.09	8.45 ± 0.12
Reticulocytes ($10^6/\mu L$)						
Day 4	0.24 ± 0.01	0.22 ± 0.01	0.19 ± 0.01*	0.21 ± 0.01*	0.23 ± 0.02	0.17 ± 0.01**
Day 24	0.17 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.01
Week 14	0.18 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.17 ± 0.01	0.15 ± 0.01	0.15 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.04 ± 0.02	0.09 ± 0.04	0.01 ± 0.01	0.09 ± 0.02	0.07 ± 0.04	0.04 ± 0.02
Day 24	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Week 14	0.02 ± 0.01	0.03 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.01 ± 0.01
Mean cell volume (fL)						
Day 4	62.4 ± 0.3	62.8 ± 0.3	62.1 ± 0.3	62.7 ± 0.2	62.3 ± 0.3	62.2 ± 0.3
Day 24	59.2 ± 0.4	58.7 ± 0.2	58.6 ± 0.1	58.6 ± 0.2	58.2 ± 0.2	58.3 ± 0.3
Week 14	55.2 ± 0.3	54.3 ± 0.1**	54.8 ± 0.3	53.8 ± 0.2**	53.3 ± 0.3**	53.0 ± 0.2**
Mean cell hemoglobin (pg)						
Day 4	21.7 ± 0.2	21.9 ± 0.2	21.8 ± 0.1	21.5 ± 0.1	21.6 ± 0.1	21.9 ± 0.1
Day 24	20.3 ± 0.1	20.5 ± 0.1	20.4 ± 0.1	20.2 ± 0.2	20.3 ± 0.1	20.5 ± 0.1
Week 14	18.4 ± 0.2	18.3 ± 0.1	18.5 ± 0.1	18.0 ± 0.1*	17.8 ± 0.1**	17.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 4	34.8 ± 0.2	34.9 ± 0.2	35.1 ± 0.2	34.4 ± 0.2	34.8 ± 0.2	35.2 ± 0.2
Day 24	34.3 ± 0.3	34.9 ± 0.2	34.8 ± 0.2	34.5 ± 0.3	35.0 ± 0.2	35.2 ± 0.2*
Week 14	33.4 ± 0.2	33.6 ± 0.2	33.7 ± 0.2	33.4 ± 0.3	33.5 ± 0.2	33.4 ± 0.2
Platelets ($10^3/\mu L$)						
Day 4	1,052.0 ± 21.2	1,016.0 ± 16.7	984.1 ± 34.8	1,020.9 ± 21.8	1,033.7 ± 34.7	964.0 ± 20.8
Day 24	808.0 ± 21.7	806.2 ± 14.2	770.2 ± 12.3	783.9 ± 8.0	776.7 ± 14.2	768.5 ± 16.1
Week 14	731.7 ± 15.9	711.8 ± 15.4	701.4 ± 19.1	672.1 ± 15.2	744.6 ± 39.0	729.5 ± 21.4
Leukocytes ($10^3/\mu L$)						
Day 4	11.47 ± 0.96	11.35 ± 0.77	10.74 ± 0.77	10.63 ± 0.41	11.26 ± 0.99	11.70 ± 0.17
Day 24	10.81 ± 0.70	10.51 ± 0.63	10.19 ± 0.95	9.60 ± 0.89	10.87 ± 0.76	10.42 ± 0.85
Week 14	7.93 ± 0.44	8.04 ± 0.44	7.59 ± 0.21	7.57 ± 0.38	8.11 ± 0.73	8.96 ± 0.78
Segmented neutrophils ($10^3/\mu L$)						
Day 4	1.35 ± 0.13	1.36 ± 0.11	1.16 ± 0.18	1.12 ± 0.10	1.41 ± 0.17	1.79 ± 0.25
Day 24	1.19 ± 0.10	1.27 ± 0.15	1.06 ± 0.12	1.01 ± 0.13	1.18 ± 0.11	1.19 ± 0.11
Week 14	1.16 ± 0.10	1.26 ± 0.11	1.00 ± 0.07	1.08 ± 0.14	1.38 ± 0.18	1.94 ± 0.21*

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Dermal Study of Coconut Oil 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	10	8	7	10	9	9
Day 24	10	10	9	7	10	10
Week 14	10	10	10	10	10	10
Lymphocytes ($10^3/\mu L$)						
Day 4	9.99 ± 0.84	9.81 ± 0.70	9.46 ± 0.76	9.37 ± 0.39	9.74 ± 0.96	9.76 ± 0.31
Day 24	9.46 ± 0.66	9.08 ± 0.52	8.92 ± 0.85	8.40 ± 0.80	9.52 ± 0.66	8.96 ± 0.73
Week 14	6.66 ± 0.38	6.70 ± 0.40	6.50 ± 0.23	6.35 ± 0.29	6.60 ± 0.53	6.77 ± 0.63
Monocytes ($10^3/\mu L$)						
Day 4	0.04 ± 0.03	0.10 ± 0.02	0.07 ± 0.04	0.06 ± 0.02	0.07 ± 0.02	0.08 ± 0.02
Day 24	0.09 ± 0.02	0.12 ± 0.04	0.07 ± 0.03	0.16 ± 0.05	0.17 ± 0.05	0.11 ± 0.03
Week 14	0.03 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.05 ± 0.02	0.03 ± 0.02	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)						
Day 4	0.09 ± 0.03	0.09 ± 0.03	0.04 ± 0.03	0.06 ± 0.02	0.03 ± 0.02	0.07 ± 0.02
Day 24	0.06 ± 0.02	0.04 ± 0.02	0.07 ± 0.03	0.04 ± 0.02	0.01 ± 0.01	0.13 ± 0.04
Week 14	0.09 ± 0.03	0.07 ± 0.03	0.10 ± 0.03	0.13 ± 0.03	0.14 ± 0.03	0.24 ± 0.06
Clinical Chemistry						
n						
Day 4	10	10	10	10	10	10
Day 24	10	10	9	10	10	10
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	23.7 ± 0.5	22.3 ± 0.7	23.0 ± 0.6	23.2 ± 0.6	23.0 ± 0.7	22.8 ± 0.2
Day 24	25.3 ± 0.4	23.5 ± 0.8	25.7 ± 0.5	25.4 ± 0.8	25.6 ± 0.8	25.2 ± 0.7
Week 14	23.8 ± 0.4	23.2 ± 0.2	23.4 ± 0.4	24.2 ± 0.5	23.5 ± 0.7	24.2 ± 0.4
Creatinine (mg/dL)						
Day 4	0.91 ± 0.02	0.87 ± 0.02	0.80 ± 0.03*	0.86 ± 0.02	0.85 ± 0.03	0.82 ± 0.01*
Day 24	0.82 ± 0.02	0.78 ± 0.02	0.78 ± 0.01	0.81 ± 0.02	0.78 ± 0.02	0.78 ± 0.01
Week 14	0.64 ± 0.02	0.60 ± 0.00	0.62 ± 0.01	0.64 ± 0.02[b]	0.63 ± 0.02[b]	0.61 ± 0.02
Total protein (g/dL)						
Day 4	6.7 ± 0.1	6.5 ± 0.1	6.4 ± 0.1	6.6 ± 0.1	6.8 ± 0.1	6.4 ± 0.1
Day 24	7.5 ± 0.2	7.4 ± 0.1	7.2 ± 0.2	7.6 ± 0.1	7.2 ± 0.1	7.3 ± 0.2
Week 14	7.0 ± 0.1	7.2 ± 0.1	7.0 ± 0.0	7.2 ± 0.1	7.1 ± 0.1[b]	7.1 ± 0.1
Albumin (g/dL)						
Day 4	4.8 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.6 ± 0.1
Day 24	5.3 ± 0.1	5.2 ± 0.1	5.1 ± 0.1	5.4 ± 0.1	5.2 ± 0.1	5.3 ± 0.1
Week 14	4.8 ± 0.0	5.0 ± 0.0*	4.9 ± 0.0	5.1 ± 0.1**	5.0 ± 0.1**[b]	5.1 ± 0.0**
Cholesterol (mg/dL)						
Day 4	100 ± 3	94 ± 2	95 ± 3	99 ± 3	96 ± 2	86 ± 2**
Day 24	94 ± 2	93 ± 2	90 ± 2	90 ± 4	82 ± 2**	77 ± 3**
Week 14	102 ± 3	99 ± 3	95 ± 3	97 ± 3	87 ± 2**	74 ± 2**
Triglycerides (mg/dL)						
Day 4	249 ± 16	227 ± 11	228 ± 15	241 ± 10	255 ± 20	220 ± 15
Day 24	328 ± 25	334 ± 30	363 ± 15	267 ± 32	340 ± 27	258 ± 24[b]
Week 14	340 ± 17	319 ± 26	384 ± 18	367 ± 21	261 ± 24*	174 ± 11**

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male (continued)						
Clinical Chemistry (continued)						
n						
Day 4	10	10	10	10	10	10
Day 24	10	10	9	10	10	10
Week 14	10	10	10	10	10	10
Alanine aminotransferase (IU/L)						
Day 4	53 ± 2	48 ± 2	49 ± 3	50 ± 1	53 ± 3	49 ± 1
Day 24	58 ± 2	50 ± 1	54 ± 2	56 ± 6	49 ± 1*	55 ± 3
Week 14	48 ± 2	50 ± 2	54 ± 2*	58 ± 3*	57 ± 5*	70 ± 4**
Alkaline phosphatase (IU/L)						
Day 4	1,639 ± 30	1,591 ± 38	1,549 ± 29	1,599 ± 26	1,582 ± 44	1,524 ± 48
Day 24	1,230 ± 34	1,127 ± 22	1,145 ± 21	1,156 ± 27	1,097 ± 25*	1,161 ± 31
Week 14	553 ± 10	566 ± 16	585 ± 11	554 ± 12	509 ± 44	617 ± 12**
Sorbitol dehydrogenase (IU/L)						
Day 4	19 ± 2	19 ± 1	19 ± 3	20 ± 2	21 ± 2	19 ± 1
Day 24	25 ± 2	21 ± 2	21 ± 2	23 ± 3	18 ± 1*	20 ± 1
Week 14	23 ± 1	21 ± 1	24 ± 1	22 ± 2[b]	21 ± 1	19 ± 1
Bile salts (μm/L)						
Day 4	54.9 ± 8.9	61.8 ± 8.3	44.2 ± 5.5	57.3 ± 9.4	49.8 ± 4.3	46.4 ± 14.2
Day 24	37.1 ± 4.1	42.7 ± 5.9	40.2 ± 4.8	52.3 ± 9.0	41.0 ± 5.1	44.5 ± 8.1
Week 14	19.9 ± 0.5	19.6 ± 1.3	21.7 ± 1.4	21.4 ± 0.6	20.5 ± 0.5	20.3 ± 1.2
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 4	47.8 ± 0.5	49.0 ± 0.7	47.2 ± 0.8	48.2 ± 1.4	48.3 ± 0.5	47.2 ± 0.5
Day 24	49.0 ± 0.5	49.5 ± 0.6	49.8 ± 0.8	48.4 ± 0.7	47.1 ± 0.7	46.7 ± 0.4*
Week 14	47.5 ± 0.5	47.9 ± 0.5	46.8 ± 0.3	45.5 ± 0.6*	43.1 ± 1.2**	42.2 ± 0.6**
Hemoglobin (g/dL)						
Day 4	16.2 ± 0.2	16.5 ± 0.2	16.1 ± 0.2	16.4 ± 0.4	16.3 ± 0.2	16.1 ± 0.2
Day 24	16.7 ± 0.1	17.0 ± 0.2	17.0 ± 0.2	16.7 ± 0.2	16.4 ± 0.2	16.3 ± 0.1
Week 14	15.9 ± 0.2	16.2 ± 0.1	15.9 ± 0.1	15.4 ± 0.2*	14.5 ± 0.4**	14.2 ± 0.2**
Erythrocytes (10^6/μL)						
Day 4	7.41 ± 0.09	7.65 ± 0.13	7.40 ± 0.13	7.53 ± 0.20	7.53 ± 0.09	7.31 ± 0.08
Day 24	7.84 ± 0.08	7.96 ± 0.10	8.11 ± 0.11	7.85 ± 0.11	7.68 ± 0.11	7.63 ± 0.07
Week 14	7.99 ± 0.10	8.08 ± 0.08	7.97 ± 0.04	7.77 ± 0.09	7.43 ± 0.18**	7.38 ± 0.09**
Reticulocytes (10^6/μL)						
Day 4	0.31 ± 0.02	0.30 ± 0.02	0.27 ± 0.02	0.30 ± 0.03	0.32 ± 0.03	0.32 ± 0.02
Day 24	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.11 ± 0.01
Week 14	0.10 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.11 ± 0.03	0.09 ± 0.01
Nucleated erythrocytes (10^3/μL)						
Day 4	0.02 ± 0.01	0.04 ± 0.02	0.11 ± 0.04	0.11 ± 0.03	0.05 ± 0.02	0.06 ± 0.03
Day 24	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00[b]	0.05 ± 0.02	0.03 ± 0.02	0.00 ± 0.00	0.03 ± 0.02	0.05 ± 0.02

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Female (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Mean cell volume (fL)						
Day 4	64.6 ± 0.3	64.1 ± 0.2	63.8 ± 0.4	64.0 ± 0.2	64.2 ± 0.2	64.6 ± 0.2
Day 24	62.5 ± 0.2	62.2 ± 0.3	61.4 ± 0.4*	61.7 ± 0.3*	61.3 ± 0.2**	61.2 ± 0.4**
Week 14	59.5 ± 0.2	59.3 ± 0.2	58.7 ± 0.3*	58.5 ± 0.2**	58.0 ± 0.3**	57.1 ± 0.2**
Mean cell hemoglobin (pg)						
Day 4	21.9 ± 0.0	21.7 ± 0.2	21.8 ± 0.1	21.8 ± 0.1	21.7 ± 0.1	22.0 ± 0.1
Day 24	21.3 ± 0.1	21.4 ± 0.1	21.0 ± 0.2	21.3 ± 0.2	21.4 ± 0.1	21.4 ± 0.2
Week 14	19.9 ± 0.1	20.0 ± 0.1	19.9 ± 0.1	19.8 ± 0.1	19.6 ± 0.2	19.3 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 4	33.8 ± 0.2	33.8 ± 0.3	34.1 ± 0.2	34.0 ± 0.3	33.8 ± 0.2	34.0 ± 0.2
Day 24	34.1 ± 0.2	34.4 ± 0.2	34.2 ± 0.2	34.5 ± 0.3	34.8 ± 0.2*	34.9 ± 0.2**
Week 14	33.6 ± 0.2	33.8 ± 0.2	33.9 ± 0.1	33.8 ± 0.1	33.7 ± 0.2	33.8 ± 0.2
Platelets ($10^3/\mu L$)						
Day 4	917.6 ± 13.8	963.2 ± 20.7	911.8 ± 16.6	950.8 ± 18.6	962.6 ± 11.9	935.7 ± 16.9
Day 24	718.1 ± 10.3	750.9 ± 12.4	720.8 ± 13.7	760.6 ± 12.3	735.9 ± 21.9	704.9 ± 15.5
Week 14	719.5 ± 53.7	628.0 ± 14.3	676.1 ± 19.3	675.4 ± 12.2	651.2 ± 17.4	697.8 ± 80.9
Leukocytes ($10^3/\mu L$)						
Day 4	10.80 ± 0.40	9.94 ± 0.62	10.03 ± 0.48	9.87 ± 0.38	10.09 ± 0.63	11.32 ± 0.58
Day 24	6.47 ± 0.32	7.25 ± 0.60	7.55 ± 0.58	7.35 ± 0.58	7.77 ± 0.43*	8.58 ± 0.60**
Week 14	7.02 ± 0.40[b]	7.16 ± 0.38	6.80 ± 0.23	6.75 ± 0.35	7.29 ± 0.28	8.19 ± 0.65
Segmented neutrophils ($10^3/\mu L$)						
Day 4	1.21 ± 0.12	0.92 ± 0.09	1.01 ± 0.12	1.21 ± 0.22	1.03 ± 0.19	1.55 ± 0.18
Day 24	0.75 ± 0.09	0.75 ± 0.07	0.60 ± 0.06	0.72 ± 0.07	0.88 ± 0.12	1.36 ± 0.20**
Week 14	1.02 ± 0.08[b]	0.93 ± 0.10	0.86 ± 0.08	0.80 ± 0.10	1.40 ± 0.15	1.90 ± 0.30**
Lymphocytes ($10^3/\mu L$)						
Day 4	9.32 ± 0.36	8.76 ± 0.55	8.82 ± 0.40	8.51 ± 0.35	8.74 ± 0.50	9.56 ± 0.51
Day 24	5.56 ± 0.31	6.29 ± 0.55	6.81 ± 0.52	6.49 ± 0.54	6.67 ± 0.33	6.95 ± 0.44
Week 14	5.87 ± 0.34[b]	6.11 ± 0.32	5.85 ± 0.22	5.86 ± 0.28	5.68 ± 0.23	6.08 ± 0.39
Monocytes ($10^3/\mu L$)						
Day 4	0.17 ± 0.05	0.21 ± 0.05	0.18 ± 0.04	0.12 ± 0.03	0.22 ± 0.06	0.09 ± 0.03
Day 24	0.08 ± 0.03	0.10 ± 0.02	0.12 ± 0.04	0.08 ± 0.02	0.15 ± 0.04	0.18 ± 0.04
Week 14	0.09 ± 0.03[b]	0.07 ± 0.02	0.07 ± 0.02	0.08 ± 0.03	0.04 ± 0.02	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)						
Day 4	0.07 ± 0.03	0.04 ± 0.02	0.04 ± 0.02	0.06 ± 0.03	0.11 ± 0.04	0.12 ± 0.04
Day 24	0.08 ± 0.02	0.10 ± 0.03	0.02 ± 0.01	0.07 ± 0.02	0.06 ± 0.02	0.11 ± 0.03
Week 14	0.08 ± 0.03[b]	0.05 ± 0.02	0.07 ± 0.02	0.06 ± 0.03	0.16 ± 0.05	0.25 ± 0.04**
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 4	23.5 ± 0.9	24.8 ± 0.8	23.8 ± 1.0	22.6 ± 0.9	22.3 ± 0.6	23.2 ± 0.7
Day 24	25.2 ± 0.7	25.5 ± 0.4	25.9 ± 0.6	26.5 ± 0.4	27.1 ± 0.4*	30.4 ± 0.7**
Week 14	23.8 ± 0.5	26.2 ± 0.6*	24.9 ± 0.6	23.0 ± 0.4	27.0 ± 1.1**	30.0 ± 0.7**
Creatinine (mg/dL)						
Day 4	0.79 ± 0.01	0.75 ± 0.02	0.70 ± 0.02*	0.72 ± 0.04	0.71 ± 0.03	0.74 ± 0.03
Day 24	0.69 ± 0.02	0.71 ± 0.02	0.73 ± 0.02	0.69 ± 0.03	0.69 ± 0.02	0.75 ± 0.02
Week 14	0.62 ± 0.01	0.63 ± 0.02	0.66 ± 0.03	0.61 ± 0.01	0.63 ± 0.04	0.64 ± 0.02

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Female (continued)						
n	10	10	10	10	10	10
Clinical Chemistry (continued)						
Total protein (g/dL)						
Day 4	6.4 ± 0.1	6.5 ± 0.1	6.1 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.1
Day 24	6.3 ± 0.1	6.3 ± 0.2	6.2 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.7 ± 0.1
Week 14	6.5 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	6.9 ± 0.1**	7.1 ± 0.1**
Albumin (g/dL)						
Day 4	4.6 ± 0.1	4.7 ± 0.1	4.4 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	4.6 ± 0.0
Day 24	4.5 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	5.3 ± 0.1**
Week 14	4.6 ± 0.0	4.8 ± 0.1*	4.8 ± 0.0**	5.0 ± 0.1**	5.2 ± 0.1**	5.4 ± 0.1**
Cholesterol (mg/dL)						
Day 4	109 ± 3	110 ± 4	102 ± 3	110 ± 4	103 ± 3	94 ± 3**
Day 24	95 ± 2	91 ± 3	84 ± 2**	80 ± 3**	71 ± 2**	64 ± 2**
Week 14	100 ± 3	94 ± 3	92 ± 3	79 ± 2**	75 ± 4**	66 ± 2**
Triglycerides (mg/dL)						
Day 4	177 ± 12	183 ± 12	178 ± 15	211 ± 15	173 ± 16	193 ± 14
Day 24	147 ± 17	140 ± 25	174 ± 22	152 ± 20	146 ± 21	141 ± 17
Week 14	115 ± 13	178 ± 21	174 ± 19	131 ± 20	143 ± 15	126 ± 22
Alanine aminotransferase (IU/L)						
Day 4	45 ± 1	48 ± 2	47 ± 1	51 ± 3	50 ± 1	46 ± 2
Day 24	37 ± 2	38 ± 1	37 ± 2	36 ± 1	35 ± 2	40 ± 1
Week 14	56 ± 5	53 ± 5	64 ± 7	60 ± 7	58 ± 4	56 ± 6
Alkaline phosphatase (IU/L)						
Day 4	1,361 ± 41	1,426 ± 20	1,359 ± 29	1,421 ± 48	1,351 ± 38	1,325 ± 23
Day 24	893 ± 26	921 ± 46	876 ± 33	884 ± 28	854 ± 23	929 ± 26
Week 14	524 ± 30	579 ± 20	549 ± 16	506 ± 16	530 ± 16	592 ± 22
Sorbitol dehydrogenase (IU/L)						
Day 4	13 ± 2	16 ± 3	16 ± 1	19 ± 4	17 ± 2	16 ± 2
Day 24	19 ± 1	20 ± 2	23 ± 3	20 ± 2	20 ± 2	25 ± 2
Week 14	21 ± 1	24 ± 1	26 ± 3	28 ± 4	25 ± 2	24 ± 2
Bile salts (μm/L)						
Day 4	38.2 ± 7.5	38.6 ± 9.0	41.5 ± 6.1	43.2 ± 6.7	36.9 ± 4.4	34.6 ± 7.8
Day 24	30.9 ± 6.8	25.7 ± 3.4	33.3 ± 4.8	27.4 ± 3.4	36.5 ± 6.3	23.6 ± 4.2
Week 14	25.8 ± 2.3	31.5 ± 6.2	31.9 ± 6.4	25.2 ± 3.6	25.7 ± 3.4[b]	23.5 ± 1.3

* 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 Coconut Oil Acid Diethanolamine Condensate 202
TABLE G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate 203

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Dermal Study of Coconut Oil 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	362 ± 6	351 ± 7	345 ± 5	343 ± 11	321 ± 7**	284 ± 9**
Heart						
Absolute	1.128 ± 0.033	1.109 ± 0.035	1.068 ± 0.026	1.079 ± 0.030	1.065 ± 0.034	0.999 ± 0.025**
Relative	3.12 ± 0.09	3.16 ± 0.07	3.09 ± 0.05	3.15 ± 0.06	3.32 ± 0.06*	3.53 ± 0.04**
R. Kidney						
Absolute	1.423 ± 0.019	1.401 ± 0.029	1.419 ± 0.029	1.474 ± 0.038	1.475 ± 0.032	1.434 ± 0.030
Relative	3.93 ± 0.03	4.00 ± 0.05	4.11 ± 0.04*	4.30 ± 0.06**	4.61 ± 0.06**	5.07 ± 0.08**
Liver						
Absolute	16.831 ± 0.417	16.186 ± 0.450	16.063 ± 0.335	16.337 ± 0.612	15.689 ± 0.539	14.021 ± 0.519**
Relative	46.47 ± 0.86	46.17 ± 0.91	46.53 ± 0.85	47.54 ± 0.66	48.89 ± 1.13	49.31 ± 0.43*
Lung						
Absolute	1.862 ± 0.076	1.766 ± 0.082	1.592 ± 0.057*	1.859 ± 0.068	1.719 ± 0.060	1.560 ± 0.067*
Relative	5.16 ± 0.23	5.02 ± 0.17	4.61 ± 0.17	5.42 ± 0.12	5.36 ± 0.12	5.50 ± 0.18
R. Testis						
Absolute	1.529 ± 0.007	1.500 ± 0.015	1.538 ± 0.014	1.461 ± 0.069	1.494 ± 0.017	1.485 ± 0.022
Relative	4.23 ± 0.07	4.29 ± 0.08	4.46 ± 0.04	4.24 ± 0.12	4.67 ± 0.08**	5.26 ± 0.10**
Thymus						
Absolute	0.359 ± 0.011	0.349 ± 0.017	0.343 ± 0.013	0.346 ± 0.025	0.313 ± 0.008	0.257 ± 0.016**
Relative	0.99 ± 0.03	1.00 ± 0.05	0.99 ± 0.04	1.00 ± 0.05	0.98 ± 0.03	0.90 ± 0.04
Female						
Necropsy body wt	192 ± 3	198 ± 4	192 ± 4	194 ± 6	182 ± 3	172 ± 4**
Heart						
Absolute	0.727 ± 0.023	0.736 ± 0.020	0.716 ± 0.017	0.719 ± 0.019	0.747 ± 0.023	0.715 ± 0.018
Relative	3.79 ± 0.09	3.72 ± 0.07	3.73 ± 0.05	3.72 ± 0.11	4.11 ± 0.11*	4.17 ± 0.08**
R. Kidney						
Absolute	0.792 ± 0.016	0.848 ± 0.020*	0.884 ± 0.017**	0.941 ± 0.015**	0.985 ± 0.015**	1.006 ± 0.027**
Relative	4.13 ± 0.06	4.29 ± 0.05	4.61 ± 0.07**	4.88 ± 0.15**	5.43 ± 0.08**	5.86 ± 0.10**
Liver						
Absolute	7.712 ± 0.263	7.813 ± 0.238	7.639 ± 0.151	8.057 ± 0.174	8.007 ± 0.089	8.452 ± 0.247
Relative	40.19 ± 1.16	39.50 ± 0.60	39.85 ± 0.70	41.64 ± 0.55	44.17 ± 0.46**	49.27 ± 1.16**
Lung						
Absolute	1.297 ± 0.028	1.282 ± 0.055	1.367 ± 0.042	1.282 ± 0.047	1.185 ± 0.032	1.112 ± 0.037**
Relative	6.76 ± 0.08	6.50 ± 0.29	7.13 ± 0.23	6.67 ± 0.34	6.55 ± 0.21	6.51 ± 0.28
Thymus						
Absolute	0.246 ± 0.009	0.252 ± 0.011	0.259 ± 0.006	0.271 ± 0.011	0.225 ± 0.008	0.204 ± 0.003**
Relative	1.28 ± 0.04	1.28 ± 0.05	1.35 ± 0.04	1.40 ± 0.05	1.24 ± 0.04	1.19 ± 0.03

* 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).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Dermal Study of Coconut Oil 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	38.8 ± 1.3	37.3 ± 0.6	37.0 ± 0.9	37.8 ± 1.1	38.6 ± 1.3	38.1 ± 1.3
Heart						
Absolute	0.197 ± 0.008	0.182 ± 0.004	0.190 ± 0.007	0.190 ± 0.004	0.195 ± 0.006	0.197 ± 0.005
Relative	5.10 ± 0.21	4.88 ± 0.11	5.12 ± 0.11	5.06 ± 0.17	5.11 ± 0.22	5.21 ± 0.19
R. Kidney						
Absolute	0.367 ± 0.008	0.369 ± 0.007	0.364 ± 0.010	0.381 ± 0.011	0.395 ± 0.009	0.424 ± 0.013**
Relative	9.51 ± 0.17	9.87 ± 0.15	9.84 ± 0.20	10.16 ± 0.39	10.30 ± 0.27*	11.16 ± 0.27**
Liver						
Absolute	1.963 ± 0.075	1.887 ± 0.055	0.048 ± 0.002	1.950 ± 0.039	2.088 ± 0.068	2.156 ± 0.075*
Relative	50.65 ± 1.04	50.49 ± 1.02	1.29 ± 0.04	51.73 ± 0.68	54.23 ± 1.09**	56.67 ± 0.85**
Lung						
Absolute	0.236 ± 0.011	0.231 ± 0.007	0.244 ± 0.006	0.251 ± 0.012	0.249 ± 0.009	0.239 ± 0.009
Relative	6.12 ± 0.29	6.21 ± 0.21	6.62 ± 0.21	6.65 ± 0.25	6.49 ± 0.23	6.34 ± 0.28
R. Testis						
Absolute	0.122 ± 0.002	0.122 ± 0.002	0.122 ± 0.002	0.122 ± 0.002	0.122 ± 0.004	0.122 ± 0.002
Relative	3.16 ± 0.06	3.26 ± 0.06	3.30 ± 0.07	3.25 ± 0.07	3.19 ± 0.11	3.23 ± 0.08
Thymus						
Absolute	0.047 ± 0.004	0.045 ± 0.003	0.048 ± 0.002	0.046 ± 0.002	0.048 ± 0.003	0.047 ± 0.003
Relative	1.20 ± 0.09	1.21 ± 0.08	1.29 ± 0.04	1.22 ± 0.07	1.24 ± 0.05	1.23 ± 0.05
Female						
Necropsy body wt	31.5 ± 0.8	32.4 ± 0.8	32.9 ± 1.0	29.8 ± 0.4	31.2 ± 0.3	30.1 ± 0.5
Heart						
Absolute	0.154 ± 0.004	0.156 ± 0.005	0.147 ± 0.004	0.161 ± 0.006	0.158 ± 0.006	0.157 ± 0.004
Relative	4.94 ± 0.20	4.82 ± 0.18	4.51 ± 0.15	5.40 ± 0.22	5.05 ± 0.18	5.23 ± 0.13
R. Kidney						
Absolute	0.237 ± 0.006	0.246 ± 0.004	0.248 ± 0.005	0.239 ± 0.005	0.248 ± 0.006	0.258 ± 0.003*
Relative	7.56 ± 0.19	7.61 ± 0.13	7.58 ± 0.20	8.01 ± 0.18	7.95 ± 0.14	8.59 ± 0.15**
Liver						
Absolute	1.602 ± 0.048	1.674 ± 0.032	1.690 ± 0.046	1.659 ± 0.040	1.808 ± 0.040**	1.866 ± 0.047**
Relative	51.07 ± 1.60	51.74 ± 0.87	51.76 ± 1.75	55.58 ± 1.10*	58.00 ± 1.15**	61.98 ± 0.96**
Lung						
Absolute	0.208 ± 0.006	0.222 ± 0.008	0.237 ± 0.011	0.216 ± 0.006	0.231 ± 0.010	0.246 ± 0.013**
Relative	6.61 ± 0.14	6.86 ± 0.22	7.24 ± 0.36	7.26 ± 0.22	7.41 ± 0.34	8.16 ± 0.42**
Thymus						
Absolute	0.058 ± 0.003	0.062 ± 0.004	0.059 ± 0.002	0.057 ± 0.003	0.055 ± 0.001	0.053 ± 0.002
Relative	1.84 ± 0.10	1.91 ± 0.10	1.81 ± 0.10	1.91 ± 0.09	1.77 ± 0.05	1.77 ± 0.05

* 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

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TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg
n	10	9	10	10
Weights (g)				
Necropsy body wt	362 ± 6	343 ± 11[b]	321 ± 7**	284 ± 9**
L. cauda epididymis	0.1559 ± 0.0056	0.1550 ± 0.0055	0.1520 ± 0.0032	0.1470 ± 0.0039
L. epididymis	0.4655 ± 0.0087	0.4533 ± 0.0059	0.4400 ± 0.0052*	0.4250 ± 0.0081**
L. testis	1.5943 ± 0.0220	1.6001 ± 0.0204	1.5605 ± 0.0244	1.5499 ± 0.0213
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.68 ± 0.18	9.03 ± 0.18	9.36 ± 0.26	9.74 ± 0.24
Spermatid heads (10^7/testis)	15.42 ± 0.34	14.45 ± 0.35	14.56 ± 0.25	15.08 ± 0.38
Spermatid count (mean/10^{-4} mL suspension)	77.10 ± 1.71	72.25 ± 1.75	72.80 ± 1.23	75.38 ± 1.89
Epididymal spermatozoal measurements				
Motility (%)	68.45 ± 1.02	65.68 ± 1.40	68.59 ± 2.12	67.29 ± 1.39
Concentration (10^6/g cauda epididymal tissue)	1,084 ± 49	1,065 ± 37	1,109 ± 60	1,111 ± 54

* Significantly different (P≤0.05) from the vehicle control group by Williams' test
** P≤0.01
[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (left cauda epididymis and left testis weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).
[b] n=10

TABLE H2
Summary of Estrous Cycle Characterization for Female Rats in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg
n	10	10	10	10
Necropsy body wt (g)	192 ± 3	194 ± 6	182 ± 3	172 ± 4**
Estrous cycle length (days)	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00[b]	5.06 ± 0.06[b]
Estrous stages (% of cycle)				
Diestrus	39.2	38.3	35.8	47.5
Proestrus	10.8	19.2	15.8	13.3
Estrus	30.8	25.8	29.2	20.0
Metestrus	19.2	16.7	19.2	19.2

** Significantly different (P≤0.01) from the vehicle control group by Williams' test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Dermal Study of Coconut Oil 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	38.8 ± 1.3	37.8 ± 1.1	38.6 ± 1.3	38.1 ± 1.3
L. cauda epididymis	0.0147 ± 0.0007	0.0150 ± 0.0008	0.0142 ± 0.0006	0.0165 ± 0.0005
L. epididymis	0.0433 ± 0.0007	0.0432 ± 0.0008	0.0431 ± 0.0014	0.0440 ± 0.0016
L. testis	0.1178 ± 0.0025	0.1173 ± 0.0027	0.1157 ± 0.0041	0.1191 ± 0.0016
Spermatid measurements				
Spermatid heads (10^7/g testis)	22.31 ± 0.49	22.77 ± 0.56	22.04 ±0.59	21.47 ± 0.51
Spermatid heads (10^7/testis)	2.63 ± 0.09	2.66 ± 0.04	2.54 ± 0.09	2.56 ± 0.06
Spermatid count (mean/10^{-4} mL suspension)	82.18 ± 2.72	83.13 ± 1.38	79.40 ± 2.97	79.85 ± 2.01
Epididymal spermatozoal parameters				
Motility (%)	64.21 ± 1.42	66.57 ± 0.58	69.97 ± 1.96	67.02 ± 1.36
Concentration (10^6/g cauda epididymal tissue)	1,664 ± 121	1,981 ± 224	1,977 ± 131	2,289 ± 111*

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

TABLE H4
Summary of Estrous Cycle Characterization for Female Mice in the 14-Week Dermal Study of Coconut Oil Acid Diethanolamine Condensate[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
n	10	10	10	10
Necropsy body wt (g)	31.5 ± 0.7	29.8 ± 0.4	31.2 ± 0.3	30.1 ± 0.5
Estrous cycle length (days)	4.30 ± 0.13	4.70 ± 0.39	4.25 ± 0.13	4.35 ± 0.15
Estrous stages (% of cycle)				
Diestrus	26.7	24.2	30.0	25.8
Proestrus	22.5	21.7	19.2	21.7
Estrus	28.3	32.5	27.5	29.2
Metestrus	22.5	21.7	23.3	23.3

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

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Coconut Oil Acid Diethanolamine Condensate

Coconut oil acid diethanolamine condensate was obtained from Henkel Corporation (Mauldin, SC) in one lot (1G01742286), 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 coconut oil acid diethanolamine condensate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a viscous yellow liquid, was identified as coconut oil acid diethanolamine condensate by infrared and nuclear magnetic resonance (NMR) spectroscopy. The spectra were consistent with those expected for the proposed compounds in the structure of coconut oil acid diethanolamine condensate and with those of a previously analyzed lot (D542578C0) not used in the current studies (MRI, 1978). The infrared spectrum contained an additional absorbance, characteristic of amine salts; the NMR spectrum indicated the presence of unreacted diethanolamine and some unsaturated salts. The infrared and nuclear magnetic spectra are presented in Figures I1 and I2.

The purity of lot 1G01742286 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 two solvent systems: A) methanol and water (80:20) and B) methanol. The flow rate was 0.5 mL/minute. ThermedeTec, Inc. (Woburn, MA), analyzed polar and nonpolar nitrosamines by HPLC with a thermo-energy analyzer.

HPLC indicated one major peak and 15 smaller peaks with areas of 0.5% or greater relative to the major peak area. Lot 1G01742286 was composed primarily of diethanolamides of coconut oil acids, with unreacted diethanolamine, alkanolamides of unsaturated acids, and amine salts of the acids. The polar nitrosamine, *N*-nitrosodiethanolamine, was detected at a concentration of 219 ppb, which was considered consistent with the anticipated composition of commercial coconut oil acid diethanolamine condensate. No nonpolar nitrosamines were detected (detection limits: 10 ppb for volatile nitrosamines or 80 ppb for nonvolatile nitrosamines). Based on calculations using the amine value provided by the manufacturer, the unreacted diethanolamine content was estimated at 18.2%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory on lot DS42578C0 using nonaqueous titration of amine function of diethanolamine with perchloric acid. Coconut oil acid diethanolamine condensate showed some instability when stored in glass tubes for 2 weeks at 60° C. 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 14 lots. The purity of the 95% ethanol used in these studies was monitored at the beginning and end of the 14-week studies and every 2 to 4 months during the 2-year studies using gas chromatography with a flame ionization detector. 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 set at 80° C for 4 minutes and then increased to 220° C at a rate of 10° C/minute. USP/NF ethanol reference standards were analyzed concomitantly. Purity of the bulk chemical ranged from 96.6% to 103.4% relative to that of the reference

standard, except for one sample taken during the 2-year studies which measured 109.6%. This was considered to be a spurious result because analysis of the same material approximately 2 months later indicated a relative purity of 101.1%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

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

Stability studies of the 10 mg/mL dose formulation were performed by the study laboratory using HPLC. When stored in sealed glass containers and protected from ultraviolet light, the stability of the dose formulations was confirmed for at least 28 days between -20° C and room temperature. When open to air and light, the stability of coconut oil acid diethanolamine condensate was confirmed for 3 hours; however, a narrow-mouth bottle was suggested for storage during dose administration to decrease evaporation of the ethanol.

Periodic analyses of the dose formulations of coconut oil 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, 13 of 15 dose formulations for rats and all 15 dose formulations for mice were within 10% of the target concentrations; two dose formulations for rats were 111% and 117% of the target concentrations. These dose formulations were remixed, and the remixes were determined to be within 10% of the target concentrations. All 48 dose formulations analyzed and used during the 2-year studies were within 10% of the target concentrations. In addition to dose formulation analysis prior to dosing, samples collected after dosing (animal room samples) were analyzed periodically. All animal room samples analyzed during the 14-week studies were within 10% of the target concentration. For the 2-year studies, 14 of 16 were within 10% of target concentration; two samples were 112% and 116% of target concentrations, apparently due to evaporation of the 95% ethanol from improperly sealed dosing bottles.

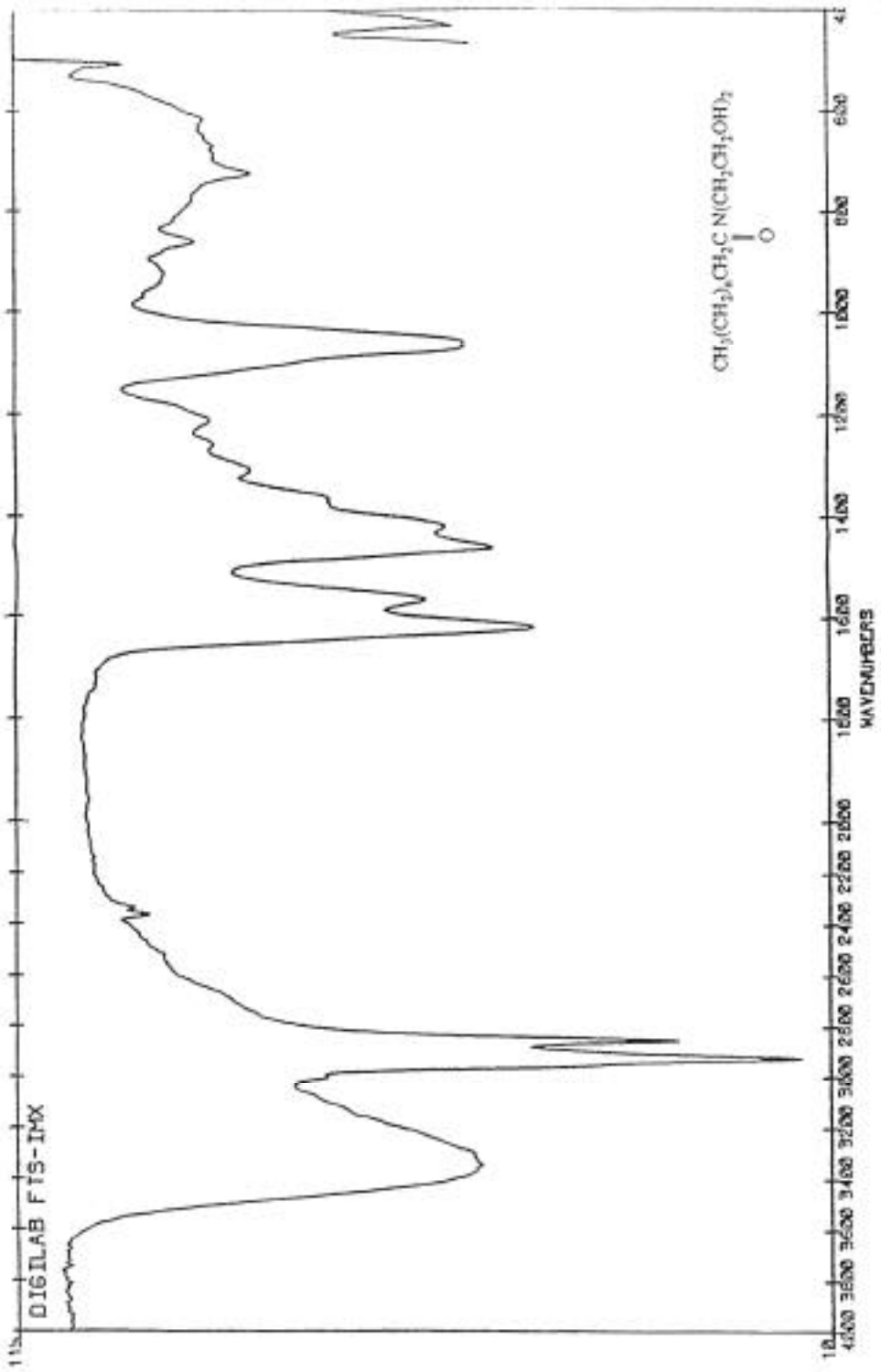

Figure I1
Infrared Absorption Spectrum of Coconut Oil Acid Diethanolamine Condensate

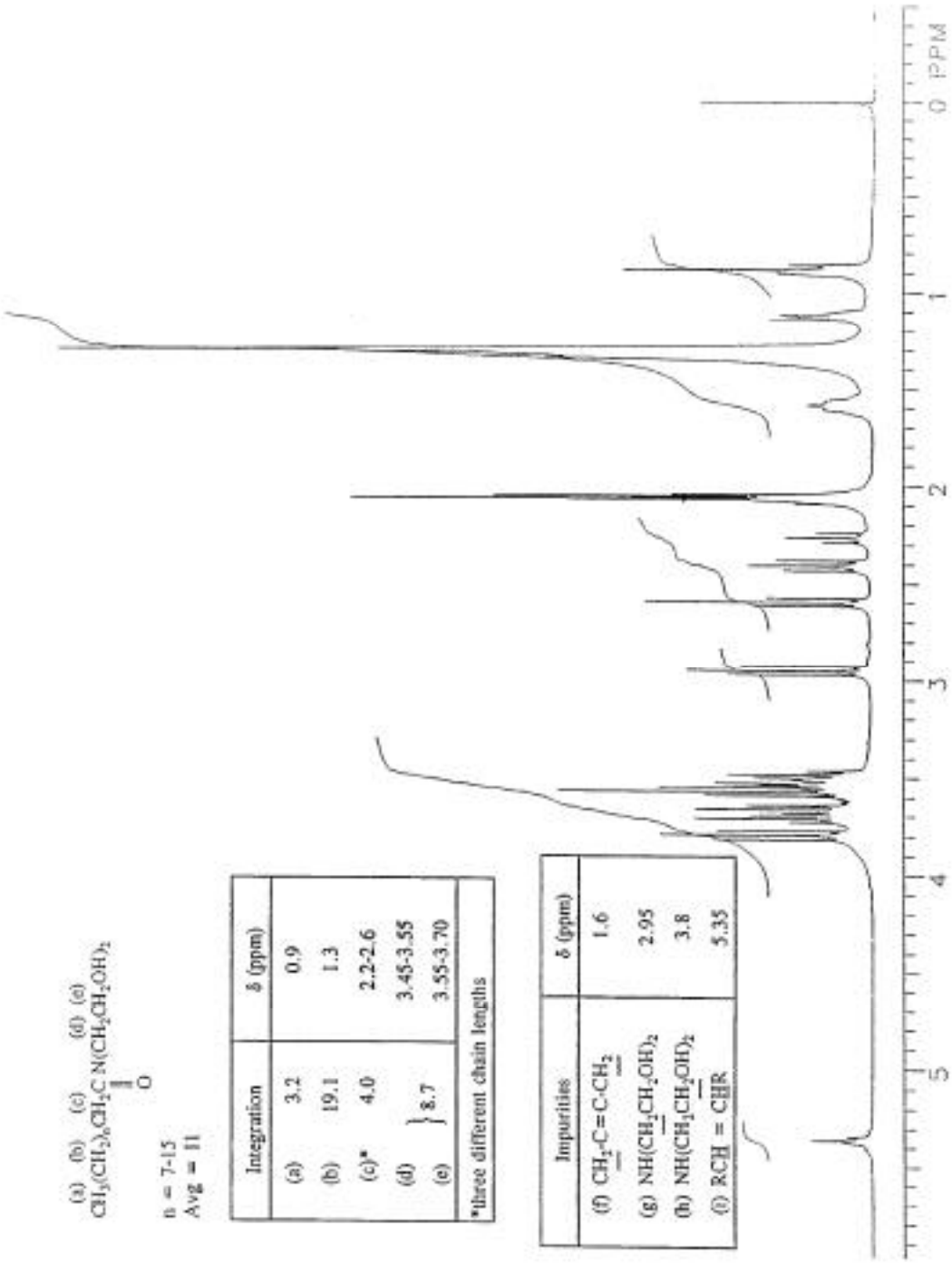

Figure I2
Nuclear Magnetic Resonance Spectrum of Coconut Oil Acid Diethanolamine Condensate

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

14-Week Studies	2-Year Studies
Preparation A weighed amount of coconut oil acid diethanolamine condensate was diluted to volume with 95% ethanol, and then the solution was thoroughly mixed by shaking. Doses were prepared every 3 weeks.	A weighed amount of coconut oil acid diethanolamine condensate was diluted with 95% ethanol. The mixture was stirred or sonicated and allowed to cool to room temperature. Additional 95% ethanol was added to obtain the final volume, and the solution was mixed by shaking. Doses were prepared every 3 weeks.
Chemical Lot Number 1G01742286	Same as 14-week studies
Maximum Storage Time 28 days	Same as 14-week studies
Storage Conditions Stored protected from light in amber glass bottles 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 Coconut Oil Acid Diethanolamine Condensate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
3 February 1992	4 February 1992	30	31.2	+4
		61	63.3	+4
		121	129	+7
		243	240	-1
		485	534	+10
	5 March 1992[b]	30	30.2	+1
		61	62.3	+2
		121	128	+6
		243	233	-4
		485	490	+1
16 March 1992	16-17 March 1992	30	29.0	-3
		61	58.9	-3
		121	120	-1
		243	241	-1
		485	485	0
	13-15 April 1992[b]	30	30.1	0
		61	61.9	+1
		121	121	0
		243	241	-1
		485	488	+1
27 April 1992	1&4 May 1992	30	30.2	+1
		61	61.9	+1
		121	120	-1
		243	270	+11
		485	568	+17
4 May 1992	5-6 May 1992[c]	243	234	-4
		485	464	-4
	18-20 May 1992[b]	30	30.2	+1
		61	63.2	+4
		121	122	+1
		243	249	+2
		485	513	+6

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

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice				
3 February 1992	4 February 1992	20	20.7	+4
		40	42.6	+7
		80	83.0	+4
		160	164	+3
		320	320	0
	5 March 1992[b]	20	20.4	+2
		40	40.0	0
		80	82.9	+4
		160	162	+1
		320	324	+1
16 March 1992	16-17 March 1992	20	21.2	+6
		40	38.8	−3
		80	79.0	−1
		160	157	−2
		320	313	−2
	13-15 April 1992[b]	20	19.8	−1
		40	40.6	+2
		80	82.0	+3
		160	160	0
		320	315	−2
27 April 1992	1&4 May 1992	20	20.4	+2
		40	40.5	+1
		80	80.9	+1
		160	161	+1
		320	340	+6
	18-20 May 1992[b]	20	19.9	0
		40	41.7	+4
		80	83.1	+4
		160	165	+3
		320	316	−1

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 117 to 285 μL (males) and 95 to 161 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 62 to 94 μL (males) and 51 to 82 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] Animal room samples
[c] Results of remix

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

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
11 January 1993	12-13 January 1993	85	82.5	−3
		170	156	−8
11 January 1993[b]	11 February 1993	85	95.5	+12
		170	185	+9
15 March 1993	15-16 March 1993	85	87.1	+2
		170	175	+3
17 May 1993	18-19 May 1993	85	85.7	+1
		170	169	−1
19 July 1993	20-24 July 1993	85	87.4	+3
		170	163	−4
19 July 1993[b]	16-17 August 1993	85	90.3	+6
		170	170	0
20 September 1993	20-21 September 1993	85	85.1	0
		170	173	+2
22 November 1993	22-23 November 1993	85	86.2	+1
		170	172	+1
24 January 1994	26-27 January 1994	85	85.4	0
		170	173	+2
24 January 1994[b]	23-24 February 1994	85	84.2	−1
		170	168	−1
28 March 1994	28-29 March 1994	85	89.9	+6
		170	182	+7
1 June 1994	1-2 June 1994	85	84.8	0
		170	169	−1
2 August 1994	2 August 1994	85	91.0	+7
		170	185	+9
2 August 1994[b]	7-8 September 1994	85	88.2	+4
		170	171	+1
3 October 1994	4-5 October 1994	85	86.2	+1
		170	175	+3
5 December 1994	6-7 December 1994	85	85.2	0
		170	172	+1

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

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice				
11 January 1993	12-13 January 1993	50	48.3	−3
		100	96.8	−3
11 January 1993[b]	11 February 1993	50	54.1	+8
		100	116	+16
15 March 1993	15-16 March 1993	50	47.9	−4
		100	103	+3
17 May 1993	18-19 May 1993	50	51.0	+2
		100	101	+1
19 July 1993	20-24 July 1993	50	46.9	−6
		100	98.8	−1
19 July 1993[b]	16-17 August 1993	50	50.5	+1
		100	97.0	−3
20 September 1993	20-21 September 1993	50	51.1	+2
		100	104	+4
22 November 1993	22-23 November 1993	50	50.5	+1
		100	103	+3
24 January 1994	26-27 January 1994	50	49.9	0
		100	102	+2
24 January 1994[b]	23-24 February 1994	50	49.9	0
		100	103	+3
28 March 1994	28-29 March 1994	50	52.9	+6
		100	109	+9
1 June 1994	1-2 June 1994	50	50.4	+1
		100	102	+2
2 August 1994	2 August 1994	50	52.5	+5
		100	107	+7
2 August 1994[b]	7-8 September 1994	50	52.9	+6
		100	104	+4
3 October 1994	4-5 October 1994	50	51.2	+2
		100	103	+3
5 December 1994	6-7 December 1994	50	50.3	+1
		100	102	+2

[a] Results of duplicate analyses. For rats, dosing volumes ranged from 76 to 274 μL (males) and 62 to 179 μL (females); 85 mg/mL=50 mg/kg and 170 mg/mL=100 mg/kg. For mice, dosing volumes ranged from 48 to 107 μL (males) and 40 to 114 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 220
TABLE J2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 220
TABLE J3 Nutrient Composition of NIH-07 Rat and Mouse Ration 221
TABLE J4 Contaminant Levels in NIH-07 Rat and Mouse Ration 222

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)	22.92 ± 0.50	22.1 – 23.9	25
Crude fat (% by weight)	5.33 ± 0.15	5.00 – 5.60	25
Crude fiber (% by weight)	3.13 ± 0.29	2.60 – 4.00	25
Ash (% by weight)	6.25 ± 0.18	5.72 – 6.64	25
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)	6,785 ± 499	6,160 – 8,800	25
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)	16.33 ± 2.42	13.0 – 24.0	24
Riboflavin (ppm)	7.78 ± 0.899	6.10 – 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0 – 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0 – 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60 – 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80 – 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190 – 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6 – 65.0	12
Choline (ppm)	2,955 ± 382	2,300 – 3,430	11
Minerals			
Calcium (%)	1.15 ± 0.06	1.03 – 1.33	25
Phosphorus (%)	0.88 ± 0.02	0.84 – 0.93	25
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)	0.51 ± 0.15	0.10 – 0.70	25
Cadmium (ppm)	0.04 ± 0.01	0.04 – 0.06	25
Lead (ppm)	0.24 ± 0.06	0.20 – 0.40	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.35 ± 0.10	0.10 – 0.50	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)[c]	7.82 ± 2.44	3.0 – 14.0	25
Nitrite nitrogen (ppm)[c]	1.19 ± 0.91	0.20 – 3.50	25
BHA (ppm)[d]	2.18 ± 4.13	0.40 – 20.0	25
BHT (ppm)[d]	1.78 ± 1.07	0.40 – 5.00	25
Aerobic plate count (CFU/g)	131,880 ± 133,954	28,000 – 460,000	25
Coliform (MPN/g)	17 ± 43.0	3 – 210	25
Escherichia coli (MPN/g)	5 ± 3.4	3 – 10	25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	12.12 ± 4.05	4.0 – 23.0	25
N-Nitrosodimethylamine (ppb)[e]	10.20 ± 4.00	3.0 – 21.0	25
N-Nitrosopyrrolidine (ppb)[e]	1.92 ± 1.16	1.0 – 6.0	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.10 ± 0.07	0.02 – 0.30	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

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

APPENDIX K
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 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	12 months and study termination
Mycoplasma pulmonis	12 months and study termination
PVM	1, 6, 12, and 18 months, study termination
RCV/SDA	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1	1, 6, 12, and 18 months, study termination
KRV	1, 6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
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-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM	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-FL	1, 6, 12, and 18 months, study termination
MHV	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Mouse adenoma virus-FL	18 months
Reovirus 3	18 months
LCM	Study termination
Hemagglutination Inhibition	
K	1, 6, 12, and 18 months, study termination
MVM	1, 6, 12, and 18 months, study termination
Polyoma virus	1, 6, 12, and 18 months, study termination

RESULTS

At the end of the 2-year studies, 6 of 10 rats and 8 of 10 mice evaluated had positive titers to *M. arthritidis*. Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

National Toxicology Program Technical Reports

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Acetaminophen	394
Acetonitrile	447
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Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
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2-Amino-5-Nitrophenol	334
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Ampicillin Trihydrate	318
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Asbestos, Amosite (Rats)	279
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Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
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Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
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Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
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1,3-Butadiene	434
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Butyl Benzyl Phthalate	458
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p-Chloroaniline Hydrochloride	351
CS2	377
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
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3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317

Chemical	TR No.
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
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3,3′-Dimethylbenzidine Dihydrochloride	390
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Dimethylvinyl Chloride	316
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Hexachloroethane	361
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
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Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
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Methyl Carbamate	328
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Methyl Methacrylate	314
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Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454
Nickel Subsulfide	453
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
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Chemical	TR No.
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435
Titanocene Dichloride	399
Toluene	371
2,4- & 2,6-Toluene Diisocyanate	251
o-Toluidine Hydrochloride	153
Triamterene	420
Tribromomethane	350
Trichloroethylene	243
Trichloroethylene	273
1,2,3-Trichloropropane	384
Tricresyl Phosphate	433
Triethanolamine	449
Tris(2-Chloroethyl) Phosphate	391
Tris(2-Ethylhexyl) Phosphate	274

Chemical	TR No.	Chemical	TR No.
Turmeric Oleoresin (Curcumin)	427	Xylenes (Mixed)	327
4-Vinylcyclohexene	303	2,6-Xylidine	278
4-Vinyl-1-Cyclohexene Diepoxide	362	Zearalenone	235
Vinylidene Chloride	228	Ziram	238
Vinyl Toluene	375		