NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 429

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIETHYLPHTHALATE (CAS NO. 84-66-2) IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

with

DERMAL INITIATION/PROMOTION STUDY OF DIETHYLPHTHALATE AND DIMETHYLPHTHALATE (CAS NO. 131-11-3) IN MALE SWISS (CD-1®) MICE

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. 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. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-3419).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIETHYLPHTHALATE (CAS NO. 84-66-2) IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

with

DERMAL INITIATION/PROMOTION STUDY OF DIETHYLPHTHALATE AND DIMETHYLPHTHALATE (CAS NO. 131-11-3) IN MALE SWISS (CD-1®) MICE

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

May 1995

NTP TR 429

NIH Publication No. 95-3356

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

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
S.L. Eustis, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
J.K. Haseman, Ph.D.
R.H. Herbert, D.V.M., Ph.D.
D.S. Marsman, D.V.M., Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Hazleton Laboratories America Inc.
Conducted studies, evaluated pathology findings

G.W. Wolfe, Ph.D., Principal Investigator
R.H. Cardy, D.V.M.
M.R. Moore, Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
H.R. Brown, M.S., D.V.M.
E. Gaillard, D.V.M., Ph.D.

Dynamac Corporation
Prepared pathology audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on rats (4 April 1991)

R.M. Sauer, V.M.D., Chair
PATHCO, Inc.
H.R. Brown, M.S., D.V.M.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
M.P. Jokinen, D.V.M
National Toxicology Program
A.W. Macklin, D.V.M., Ph.D.
Burroughs Wellcome Research Laboratories
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (14 April 1992)

P.K. Hildebrandt, D.V.M., Chair
PATHCO, Inc.
R. Cattley, M.S., V.M.D., Ph.D.
Chemical Industry Institute of Toxicology
E. Gaillard, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
R.H. Herbert, D.V.M., Ph.D.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program
K. Takahashi, D.V.M., M.Sc., Ph.D.
National Toxicology Program

Biotechnical Services, Inc.
Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
J.R. Beverly, B.A.
P. Chaffin, B.S.E.
S.R. Gunnels, M.A.
H.A. Lindsay, B.A.
E.S. Rathman, M.S.

CONTENTS

ABSTRACT 5

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 10

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 11

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 12

INTRODUCTION 13

MATERIALS AND METHODS 21

RESULTS 33

DISCUSSION AND CONCLUSIONS 63

REFERENCES 65

APPENDIX A Summary of Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate 71

APPENDIX B Summary of Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate 109

APPENDIX C Summary of Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate 147

APPENDIX D Summary of Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate 185

APPENDIX E Genetic Toxicology 227

APPENDIX F Organ Weights and Organ-Weight-to-Body-Weight Ratios 241

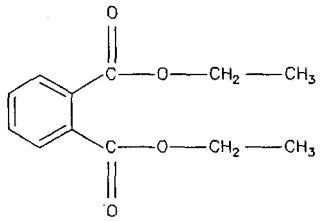
APPENDIX G Hematology and Clinical Chemistry Results 247

APPENDIX H Chemical Characterization and Dose Formulation Studies 251

APPENDIX I Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration 269

APPENDIX J Sentinel Animal Program 275

ABSTRACT

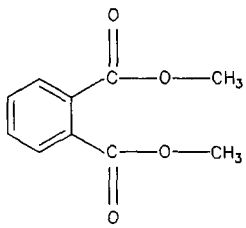


DIETHYLPHTHALATE

CAS No. 84-66-2

Chemical Formula: $C_{12}H_{14}O_4$ Molecular Weight: 222.26

Synonyms: 1,2-benzenedicarboxylic acid, diethyl ester; DEP; diethyl 1,2-benzenedicarboxylate; diethyl *o*-phthalate; diethyl phthalate; ethyl phthalate; *o*-benzenedicarboxylic acid diethyl ester; phthalic acid, diethyl ester; RCRA U088
Trade Names: Anozol; DPX-F5384; Estol 1550; Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; Unimoll DA



DIMETHYLPHTHALATE

CAS No. 131-11-3

Chemical Formula: $C_{10}H_{10}O_4$ Molecular Weight: 194.19

Synonyms: 1,2-benzenedicarboxylic acid, dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-*o*-dicarboxylate; dimethyl benzeneorthodicarboxylate; dimethyl *o*-phthalate; dimethyl phthalate; DMP; FIFRA 028002; methyl phthalate; *o*-dimethyl phthalate; phthalic acid, dimethyl ester; phthalic acid methyl ester; RCRA U102
Trade Names: Avolin; DMF (insect repellent); ENT 262; Fermine; Mipax; NTM; Palatinol M; Repeftal; Solvanom; Solvarone; Unimoll DM

Diethylphthalate and dimethylphthalate are used as phthalate plasticizers, in an extensive array of products. The chronic dermal toxicity of diethylphthalate was evaluated in male and female F344/N rats and B6C3F$_1$ mice in 2-year studies. In a series of special studies, the tumor initiation or promotion potential of diethylphthalate or dimethylphthalate was evaluated in male Swiss (CD-1®) mice by an

initiation/promotion model of skin carcinogenesis. The genetic toxicity of diethylphthalate and dimethylphthalate in *Salmonella typhimurium* and cultured Chinese hamster ovary cells was also evaluated.

4-Week Study In F344/N Rats

Groups of 10 male and 10 female rats were dermally administered diethylphthalate at volumes of 0, 37.5, 75, 150, or 300 μL (0, 46, 92, 184, or 369 μg) applied neat, 5 days per week for 4 weeks. All male and female rats survived to the end of the study. No evidence of dermatotoxicity was observed, with no adverse clinical signs observed and no effects on weight gain or feed consumption. Relative liver weights of 300 μL males and females and 150 μL females were greater than those of controls. Relative kidney weights of 150 and 300 μL males and 150 μL females were greater than those of controls. No other adverse effects were observed in this study.

4-Week Study In B6C3F$_1$ Mice

Groups of 10 male and 10 female mice were dermally administered diethylphthalate at volumes of 0, 12.5, 25, 50, or 100 μL (0, 15, 31, 62, or 123 μg) applied neat, five days per week for 4 weeks. One control female died before the end of the study; all other mice survived. No evidence of dermatotoxicity or other adverse clinical signs were observed, and no clear adverse effects on weight gain or feed consumption were seen. Absolute and relative liver weights of 25 and 100 μL females were greater than those of the controls. Based on these 4-week study results, doses of 0, 35, and 100 μL diethylphthalate were recommended for the 2-year mouse studies. A chronic study in male and female B6C3F$_1$ mice at 0, 35, and 100 μL (applied neat, once per day, 5 days per week) was started and subsequently stopped after 32 weeks when significant body weight reductions were noted in treated animals (males and females, 100 μL groups: 19% lower; males, 35 μL group: 12% lower; females, 35 μL group: 10% lower than controls). Based on these body weight reductions, doses of 0, 7.5, 15, and 30 μL in 100 μL acetone were recommended for the restart of the 2-year mouse study.

2-Year Study In F344/N Rats

Based upon the results of the 4-week study, doses of 0, 100, or 300 μL diethylphthalate (0, 123, or 369 μg) were chosen for the 2-year rat study. Groups of 60 male and 60 female rats received the doses applied neat 5 days per week for 103 weeks and up to 10 animals per group were evaluated after 15 months.

Survival, Body Weights, and Clinical Findings

Survival of dosed rats during the first 15 months was similar to that of controls. However, 2-year survival was significantly reduced in all groups of male rats (survival probabilities, males: 0 μL, 8%; 100 μL, 12%; and 300 μL, 12%). The mean body weights of 300 μL males were slightly less than those of the controls throughout the study. No adverse clinical signs were observed, including no evidence of dermatotoxicity.

Pathology Findings

No morphological evidence of dermal or systemic toxicity was observed in male or female rats. Skin neoplasms were not observed in female rats and were only rarely observed in male rats. A high incidence of anterior pituitary adenoma occurred in all groups of male and female rats. The incidence of anterior pituitary adenomas in the 0, 100, and 300 μL groups were: males, 39/44, 41/49, 41/49; females, 38/50, 33/49, 33/48. The incidence of this benign tumor in control males (84%) exceeded the historical control mean incidence [feed controls, (28.7%)] and range (12% to 60%). Anterior pituitary adenomas were considered a primary contributing factor in the increased mortality observed in all groups, regardless of treatment. A dose-related decreasing trend in the incidence of mammary gland fibroadenomas was observed in female rats (21/50, 12/48, 7/50). The incidence of mononuclear cell leukemia in male rats in this study was lower than the historical incidence and may be attributable to the shortened life span of male rats. Similarly, the incidence of interstitial cell tumors of the testes was markedly decreased in all groups of males (4/50, 3/50, 8/50), relative to historical control rates (90.1%; range 74%-98%). The incidence of fatty liver degeneration was notably lower in dosed rats than in controls (males: 26/50, 8/50, 4/51; females: 23/50, 11/50, 3/50).

2-Year Study In B6C3F$_1$ Mice

Groups of 60 male and 60 female mice received doses of 0, 7.5, 15, or 30 μL diethylphthalate (0, 9, 18, or 37 μg) in 100 μL acetone 5 days per week for 103 weeks with a 1 week recovery period, and up to 10 animals per group were evaluated after 15 months.

Survival, Body Weights, and Clinical Findings

Two-year survival of dosed mice was similar to that of controls: 43/50, 41/48, 46/50, and 43/50 (males), and 41/50, 38/51, 37/49, and 36/49 (females). Mean body weights of dosed male and female mice were similar to those of the controls throughout the study. No adverse clinical signs were observed in mice, including no gross evidence of dermatotoxicity. Feed consumption by male and female mice was similar to or up to 13% greater than that by controls.

Pathology Findings

No morphological evidence of dermal toxicity was observed in male or female mice. No skin neoplasms were observed in dosed male mice. In female mice receiving 30 μL, one squamous cell carcinoma and one basal cell carcinoma were seen at the site of application. An increased incidence of liver neoplasms was observed in dosed male and female mice. The incidence of hepatocellular adenoma or carcinoma (combined) in $B6C3F_1$ mice in the 0, 7.5, 15, and 30 μL groups were: (males) 9/50, 14/50, 14/50, and 18/50; (females) 7/50, 16/51, 19/50, and 12/50. The incidence of adenoma or carcinoma (combined) was increased in 30 μL male mice and the incidences of adenoma and of adenoma or carcinoma (combined) were increased in 7.5 and 15 μL females. A positive dose-related trend in the incidence of adenoma or carcinoma (combined) was also observed in male mice. The incidence of basophilic hepatic foci was increased in 15 μL male mice (0/50, 1/50, 9/50, 3/50). The increased incidence of liver neoplasms in this study was considered equivocal because the incidence of hepatocellular neoplasms in control and dosed males was within the historical range and because there was no clear dose-response relationship in females. No other treatment-related findings were observed in this study.

1-Year Initiation/Promotion Study In Male Swiss (CD-1®) Mice

Groups of 50 male mice were dosed dermally with diethylphthalate or dimethylphthalate to study their effect as initiators and promoters. Diethylphthalate and dimethylphthalate were tested as initiators with and without the known skin tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Diethylphthalate and dimethylphthalate were tested as promoters with and without the known skin tumor initiator 7,12-dimethylbenzanthrancene (DMBA). Comparative control groups used during the study of diethylphthalate and dimethylphthalate included: vehicle control (acetone/acetone); initiation/promotion control (DMBA/TPA); initiator control (DMBA/acetone); and promoter control (acetone/TPA).

Based on the incidence of skin neoplasms diagnosed histologically and the multiplicity of skin neoplasms, there was no suggestion that either diethylphthalate or dimethylphthalate was able to initiate skin carcinogenesis when chronically promoted by TPA. Further, there was no evidence that either diethylphthalate or dimethylphthalate was able to promote skin carcinogenesis in skin previously initiated with DMBA. High incidences of both squamous cell papillomas and squamous cell carcinomas occurred among the initiation/promotion control animals initiated with DMBA and promoted with TPA. All TPA-dosed groups had significantly greater incidences of dermal acanthosis, ulceration, exudation, and hyperkeratosis than controls.

Genetic Toxicology

Neither diethylphthalate (10-10,000 μg/plate) nor dimethylphthalate (33-6,666 μg/plate) induced gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without rat and hamster liver S9. In cultured Chinese hamster ovary cells, both diethylphthalate and dimethylphthalate induced sister chromatid exchanges in the presence of S9. Neither induced sister chromatid exchanges in the absence of S9. Neither chemical induced chromosomal aberrations, with or without S9, in cultured Chinese hamster ovary cells.

Conclusions

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diethylphthalate in male or female F344/N rats receiving 100 or 300 μL. The sensitivity of the male rat study was reduced due to low survival in all groups. There was *equivocal evidence of carcinogenic activity* of diethylphthalate in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms, primarily adenomas.

In an initiation/promotion model of skin carcinogenesis, there was no evidence of initiating activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. Further, there was no evidence of

promotion activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. The promoting activity of TPA following DMBA initiation was confirmed in these studies.

Minor dermal acanthosis was observed following dermal application of diethylphthalate in male and female F344/N rats dosed for 2 years and in male Swiss (CD-1®) mice dosed for 1 year.

---

* 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 Diethylphthalate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 100, or 300 μL diethylphthalate applied dermally	0, 100, or 300 μL diethylphthalate applied dermally	0, 7.5, 15, or 30 μL diethylphthalate per 100 μL of acetone applied dermally	0, 7.5, 15, or 30 μL diethylphthalate per 100 μL of acetone applied dermally
Body weights	High-dose group less than controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates	4/50, 6/50, 6/51	30/51, 28/50, 23/50	43/50, 41/48, 46/50, 43/50	41/50, 38/51, 37/49, 36/49
Nonneoplastic effects	Skin site of application: acanthosis (2/50, 5/50, 21/51); Liver: fatty degeneration (26/50, 8/50, 4/51)	Skin site of application: acanthosis (8/50, 18/49, 23/50); Liver: fatty degeneration (23/50, 11/50, 3/50)	Liver: basophilic foci (0/50, 1/50, 9/50, 3/50)	None
Neoplastic findings	None	None	None	None
Uncertain effects	None	None	Liver: hepatocellular adenoma (6/50, 11/50, 9/50, 12/50); hepatocellular adenoma or carcinoma (9/50, 14/50, 14/50, 18/50)	Liver: hepatocellular adenoma (4/50, 12/51, 14/50, 10/50); hepatocellular adenoma or carcinoma (7/50, 16/51, 19/50, 12/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	Equivocal evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on diethylphthalate/dimethylphthalate on November 16, 1993, 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 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.

Curtis D. Klaassen, Ph.D., Chair
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Paul T. Bailey, Ph.D., Principal Reviewer
Environmental and Health Sciences Laboratory
Mobil Oil Corporation
Princeton, NJ

Arnold L. Brown, M.D.*
University of Wisconsin Medical School
Madison, WI

Louise Ryan, Ph.D., Principal Reviewer
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Matthew J. van Zwieten, D.V.M., Ph.D.,
Principal Reviewer
Department of Safety Assessment
Merck Research Laboratories
West Point, PA

Jerrold M. Ward, D.V.M., Ph.D.
National Cancer Institute
Frederick, MD

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 16, 1993, the draft Technical Report on the toxicology and carcinogenesis studies of diethylphthalate/dimethylphthalate received public review by the National Toxicology Program 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. D.S. Marsman, NIEHS, introduced the toxicology and carcinogenesis studies of diethylphthalate and the initiation/promotion studies of diethylphthalate and dimethylphthalate. He discussed the uses of the chemical and the rationale for both studies, described the experimental designs, reported on survival and body weight effects, and commented on compound-related nonneoplastic lesions in male and female rats and male mice in the initiation/promotion study, and the compound-related neoplastic lesions in male and female mice in the 2-year studies. The proposed conclusions were *no evidence of carcinogenic activity* of diethylphthalate for male and female F344/N rats and *equivocal evidence of carcinogenic activity* of diethylphthalate for male and female B6C3F$_1$ mice. In an initiation/promotion model of skin carcinogenesis, there was no evidence of initiating or promoting activity of diethylphthalate or dimethylphthalate for male Swiss (CD-1®) mice.

Dr. Bailey, a principal reviewer, agreed with the proposed conclusions. He said the rationale for dermal application should be expanded since the main routes of exposure for humans appear to be ingestion and inhalation. Dr. Marsman said a 4-week diet study was done and a 2-year diet study was designed, but the dermal route was considered to be the most important route for humans. Dr. Bailey said a comment should be added in the discussion concerning the possibility of ingestion of diethylphthalate from grooming after dermal application. Dr. Marsman agreed that grooming might have resulted in systemic availability of chemical.

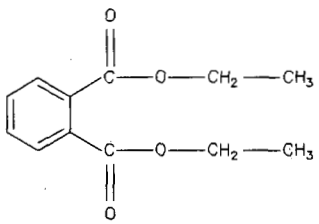
Dr. van Zwieten, the second principal reviewer, agreed with the proposed conclusions. He said a comment was needed as to why 4-week studies were done in rats and mice instead of the customary 13-week studies that might have better predicted doses for the first 2-year study in mice. Dr. Marsman said a 4-week prechronic regimen for dermal studies was preferred at the time these studies were initiated, and agreed that 13-week studies might have been more helpful in setting doses for the 2-year mouse studies. Dr. van Zwieten asked for discussion about whether an increased incidence of pituitary neoplasms might help explain the reduced survival in male rats. Dr. J.R. Hailey, NIEHS, commented that many of these neoplasms in males were quite large and could have contributed in an additive way to decreased survival along with nephropathy, which is much more severe in male rats.

Dr. Ryan, the third principal reviewer, had similar questions about choice of dermal exposure over other routes of exposure, and why 4-week instead of 13-week studies were done. She thought the dose-finding aspects for the 2-year studies to be less stringent than usual, expressing doubts that a maximum tolerated dose was reached for either rats or mice.

Dr. Ward asked whether there was evidence of peroxisome proliferation in the livers of animals in any of the studies. Dr. Marsman replied that this was not measured, although the hepatomegaly present could be suggestive of such an effect. Dr. R. David, Eastman Kodak Company, stated that they agreed with the proposed conclusions for rats but thought the proposed conclusions for mice should have been *no evidence* based in part on the incidence of hepatocellular neoplasms in treated male mice being within the historical control range, and on the lack of a dose response for liver neoplasms in female mice.

Dr. Bailey moved that the Technical Report on diethylphthalate and diethylphthalate/dimethylphthalate be accepted with the revisions discussed and with the conclusions as written for the 2-year studies for male and female rats, *no evidence of carcinogenic activity*, and for male and female mice, *equivocal evidence of carcinogenic activity*, as well as the conclusions that there was no evidence of initiating or promoting activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. Dr. Ward seconded the motion, which was accepted unanimously with five votes.

INTRODUCTION



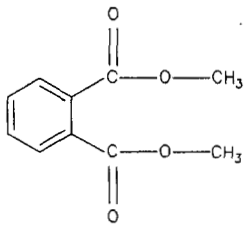
DIETHYLPHTHALATE

CAS No. 84-66-2

Chemical Formula: $C_{12}H_{14}O_4$ Molecular Weight: 222.26

Synonyms: 1,2-benzenedicarboxylic acid, diethyl ester; DEP; diethyl 1,2-benzenedicarboxylate; diethyl *o*-phthalate; diethyl phthalate; ethyl phthalate; *o*-benzenedicarboxylic acid diethyl ester; phthalic acid, diethyl ester; RCRA U088.

Trade Names: Anozol; DPX-F5384; Estol 1550; Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; Unimoll DA.



DIMETHYLPHTHALATE

CAS No. 131-11-3

Chemical Formula: $C_{10}H_{10}O_4$ Molecular Weight: 194.19

Synonyms: 1,2-benzenedicarboxylic acid, dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-*o*-dicarboxylate; dimethyl benzeneorthodicarboxylate; dimethyl *o*-phthalate; dimethyl phthalate; DMP; FIFRA 028002; methyl phthalate; *o*-dimethyl phthalate; phthalic acid, dimethyl ester; phthalic acid methyl ester; RCRA U102.

Trade Names: Avolin; DMF (insect repellent); ENT 262; Fermine; Mipax; NTM; Palatinol M; Repeftal; Solvanom; Solvarone; Unimoll DM.

CHEMICAL AND PHYSICAL PROPERTIES

Diethylphthalate (DEP) and dimethylphthalate (DMP) are aromatic diesters of phthalic anhydride and ethanol or methanol, respectively. DEP is a colorless, oily liquid with a boiling point of 295° C (*Merck Index*, 1983), a melting point of −40.5° C (Sax, 1984), and a density of 1.23 (*Merck Index*, 1983). DEP has an octanol/water partition coefficient of log K_{ow}= 2.47 (Hansch and Leo, 1979) and a vapor pressure of 1.65×10^{-3} mm Hg at 25° C (Howard *et al.*, 1985). DEP is soluble in alcohol, ether, acetone, and

benzene (Weast, 1986); miscible with vegetable oils (Lefaux, 1968), ketones, esters, and aromatic hydrocarbons; and partly miscible with aliphatic solvents (Hawley, 1981). DEP is slightly water soluble (1,080 mg/L at 25° C; Howard *et al.*, 1985).

DMP is a colorless to pale yellow, oily liquid with a slightly aromatic or ester odor at room temperature (Mackison *et al.*, 1981; *Merck Index*, 1983; Worthing and Walker, 1987). DMP has a boiling point of 283.7° C, a melting point of 5.5° C, and a density of 1.20 (*Merck Index*, 1983). DMP has a calculated octanol/water partition coefficient of log K_{ow}= 2.12 (Callahan *et al.*, 1979) and a vapor pressure of less than 0.01 mm Hg at 20° C (*Merck Index*, 1983). DMP is soluble in petroleum oils, diethyl ether, most organic solvents (Worthing and Walker, 1987), mineral oil (0.34 g/100 g at 20° C; *Merck Index*, 1983), and in benzene (Weast, 1987); is miscible with alcohol, ether, and chloroform; and is insoluble in petroleum ether and paraffin hydrocarbons (*Merck Index*, 1983). DMP is moderately water soluble (0.43 g/dL; *Merck Index*, 1983).

USE AND HUMAN EXPOSURE

As phthalate plasticizers, DEP and DMP are used in a variety of plasticized, cellulose-based products such as safety glass, toothbrushes, and toys. Among the cosmetics reportedly containing DEP or DMP are bath preparations, eye shadows, perfumes and fragrances, hair sprays, wave sets, and nail polishes (concentration range: 0.1% to 50%) (Kamrin and Mayor, 1991). In addition, other nonplasticized products such as solvents, varnishes, dyes, perfumes, coating agents for foodstuffs, and insect repellants contain considerable amounts of DEP and/or DMP as primary ingredients or as carriers.

The diverse uses of DEP and DMP provide numerous routes for their entrance into the environment. DEP may enter the environment in air emissions, in aqueous effluent and solid waste products from manufacturing and processing plants, in vapor or particulate form during incineration of DEP-containing plastics, or DEP may enter the environment directly during non-plasticizer use. Plastic materials containing DEP in waste disposal sites constitute the major reservoir of this compound in the environment. It is estimated that as much as 75% of the total environmental release of phthalates (including DEP and DMP) results from low-temperature burning at disposal sites with the subsequent vaporization of the phthalates (ATSDR, 1993). Direct volatilization and leaching from these materials are also potential sources of transport into air, water, and soil. If released to water, DEP and DMP are expected to biodegrade with an aerobic biodegradation half-life estimated at approximately 1 day to greater than 2 weeks. In contrast, anaerobic biodegradation occurs very slowly or not at all. Diethylphthalate has accumulated and persisted in the sediments of Chesapeake Bay for over a century (Peterson and Freeman, 1982). Data collected on phthalates from field and laboratory studies indicate that bioaccumulation is possible by a variety of organisms. However, the phthalates are degraded by microbiota and metabolized by fish and animals. Thus, they are not expected to biomagnify and the highest concentrations would be expected at intermediate levels of the food chain (i.e., invertebrates) rather than at the top (Kayser *et al.*, 1982). DMP (versus DEP) is more likely to degrade under anaerobic conditions and is less likely to bioconcentrate in fish.

The potential for human exposure to DEP and DMP is great. Exposure can occur directly through the production or use of a variety of consumer goods and indirectly through water supplies and the consumption of fresh and processed packaged foods containing the chemicals. The most probable routes of human exposure to DEP or DMP are occupational exposure via inhalation and dermal exposure by workers involved in the manufacture and use of these chemicals. A National Occupational Exposure Survey (NIOSH, 1990) estimated that 239,150 workers were potentially exposed to DEP and 57,910 workers were potentially exposed to DMP. The most probable routes of exposure to DEP or DMP by the general population are inhalation, ingestion, and dermal contact due to use of consumer products containing these chemicals. DEP has been identified as a suspected contaminant or environmental pollutant in a variety of foodstuffs: cranberries, baked potatoes, roasted filberts, oysters, clams, and fish (DeVault, 1985; McFall *et al.*, 1985; Staples *et al.*, 1985). DEP has been detected in adipose tissue of people (including children) (ATSDR, 1993). United States production of DEP in 1985 was approximately 7.8 million kg (USITC, 1985), and in 1988 had risen to 9.5 million kg (Kamrin and Mayor, 1991). An additional 0.2 million kg of DEP was imported (SRI, 1991).

DMP has a reported U.S. production of approximately 3.5 million kg (USITC, 1985).

Regulatory Status

In addition to the EPA's Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (Superfund) status, the Food and Drug Administration has classified both DEP and DMP as migratory, indirect food additives. The Occupational Safety and Health Administration has designated DEP and DMP as chemicals for study under an Interagency Testing Committee. The permissible threshold limit value-time weighted average level for DEP or DMP is 5 mg/m^3 (ACGIH, 1991).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

The phthalate esters are readily absorbed from the gastrointestinal tract (International Labour Office, 1983), the peritoneal cavity, the lungs (USEPA, 1980), and the skin (Elsisi *et al.*, 1989). In rodents, DEP is absorbed following dermal exposure, with 24% of the dose excreted in the urine in the first 24 hours (Elsisi *et al.*, 1989). In a comparison with DMP and five other diester phthalates, skin absorption was inversely associated with length of the aliphatic side-chain, with absorption favoring the shorter-chain phthalates (i.e., DMP and DEP).

After oral administration of [^{14}C]-labeled DEP or DMP to rats or mice, radioactivity was found in the blood and various tissues, as well as in the placenta and fetal tissues when given to pregnant dams (Singh *et al.*, 1975). Maximum values for radioactivity were observed within 1 hour. Tissue radioactivity was highest in the kidneys, followed in decreasing order by the liver, fat, and spleen. After 24 hours, 90.9% of the administered dose of DMP had been excreted in the urine and 4.1% in the feces (Ioku *et al.*, 1976). Studies with DEP and DMP have identified the major urinary metabolite to be the monoester, monoethylphthalate or monomethylphthalate, respectively, although some free acid was found (Hathway, 1972; Menzie, 1974). The monoesters were 4 times more toxic than the original substances. There is some suggestion that the phthalates with a short alcohol chain (such as DEP or DMP) have a higher acute toxicity due to a more rapid cleavage to form the putative active metabolite monoesters (International Labour Office, 1983). Alternatively, some of the toxicity may also be due to the other cleavage products, ethanol or methanol, respectively, or their subsequent metabolites (Kozumbo and Rubin, 1991). Both hepatic and intestinal preparations from rats, ferrets, baboons, and humans were effective in hydrolyzing phthalates (including DEP and DMP) to their corresponding monoester derivatives (Lake *et al.*, 1977). Again, little of the free acid or of other metabolites were found and, in general, loss of the second alkyl residue or other modifications of the monoester are presumed to be minor.

Humans

In vitro models of dermal absorption suggest that both DEP and DMP are absorbed in both rats and humans, with human epidermal membranes somewhat less permeable than rats (Scott *et al.*, 1987). DMP when applied to human skin was absorbed and appeared in the blood. The compound was metabolized and excreted in the urine as monomethylphthalate and phthalic acid (Gleiberman *et al.*, 1978). Human cell preparations *in vitro* suggest that humans are similar to or more effective than rodents at hydrolyzing DEP or DMP to their monoesters (Lake *et al.*, 1977).

Toxicity

Experimental Animals

The literature suggests that the acute toxicity of DEP and DMP are both low. Central nervous system effects and damage to the spleen and kidneys were seen in laboratory animals given high doses of DEP. Oral LD_{50} values reported for DEP in rats, mice, guinea pigs, and rabbits are 8,600, 6,172, 8,600, and 1,000 mg/kg, respectively (Sax, 1984). Intraperitoneal LD_{50} values with DEP in rats and mice are 5,058 and 2,749 mg/kg, respectively. Oral LD_{50} values reported for DMP in rats, mice, guinea pigs, rabbits, and chickens are 8,400, 6,800, 2,400, 4,400, and 8,500 mg/kg, respectively (Autian, 1973). Intraperitoneal LD_{50} values with DMP in rats and mice are 3,375 and 1,380 mg/kg, respectively. Dermal LD_{50} values for DMP in guinea pigs and rabbits were at or above 10,000 mg/kg.

In the liquid form, DEP is a mild irritant to guinea pig skin and rabbit eyes, and irritation to the respiratory passages and eyes of cats was seen following exposure to airborne DEP (BIBRA, 1989). Dermal absorption has been demonstrated in rats (Elsisi *et al.*, 1989) and humans (Gleiberman *et al.*, 1978); however, no detailed studies in animals have evaluated systemic effects following dermal applications of DEP or DMP. The most detailed subchronic study with DEP was a dietary study in which 15 male and 15 female CD rats were fed 0%, 0.2%, 1.0%, or 5.0% DEP for 16 weeks, with interim evaluations at 2 and 6 weeks (Brown *et al.*, 1978). The estimated mean intake of DEP was 0, 150, 770, and 3,160 mg/kg per day for males and 0, 150, 750, and 3,710 mg/kg per day for females. Decreases in feed consumption and body weight gain were observed in groups of rats at 5.0%. No clinical signs of toxicity were observed. No significant dose- or time-related trends in urinalysis or hematology results were found. Increases in relative liver weights were observed in males receiving 5.0% and in all exposed females at 16 weeks.

DEP is thought to be a weak liver peroxisome proliferator (Moody and Reddy, 1978). Similar evaluations have not been made for DMP, although cholesterol-lowering effects have been observed in rats, a common finding in rats fed peroxisome proliferating chemicals (USEPA, 1980). Some increases in liver cytochrome P_{450} activity were observed after 5 days of intraperitoneal dosing with DMP, although the activities were lower than the activities induced by the confirmed peroxisome proliferator, dibutylphthalate (Walseth *et al.*, 1982). In an *in vitro* study, DEP was not shown to affect the conjugating enzymes, N-acetyltransferase or cytochrome P_{450}; however, DEP was shown to inhibit the uridine diphosphate glucuronyl transferase activity of rat liver microsomal preparations (Gollamudi *et al.*, 1985).

Testicular toxicity has been observed for both DEP (Lamb *et al.*, 1987) and DMP, although not to the degree of the related testicular toxins, di(2-ethylhexyl)phthalate (NTP, 1982a) and dibutylphthalate (NTP, 1994). Dietary administration of DEP to rats for 16 weeks increased testicular weights (BIBRA, 1989), while DEP and DMP decreased serum and testicular testosterone concentrations (Oishi and Hiraga, 1980).

In a 2-year toxicity study, groups of 15 male and 15 female rats (strain not specified) were fed 0%, 0.5%, 2.5%, or 5.0% DEP in the diet. Other than growth retardation of animals in the 5.0% group, there were no other treatment-related effects on gross organ examination or histopathology (Food Research Laboratories, Inc., 1955). Similarly, a 2-year feeding study with DMP in female rats at levels of 2% to 8% in diet showed only slight growth effects at 4% and 8%, although there were some chronic nephritic changes reported at 8% (*Patty's*, 1981). Also in the chronic DEP study (Food Research Laboratories, Inc., 1955), dogs were fed DEP at levels of 0.5%, 1.5%, 2.0%, or 2.5% for one year. Problems were encountered with palatability of DEP in the diet, and as a result, the dogs received varying exposures to DEP before each dog attained stabilization at the highest dietary levels that could be tolerated. Accordingly, three dogs were maintained at 0.5%, one each at 1.5% and 2.0%, and three at 2.5%. No effects were noted at any of these levels.

Humans

In humans, DEP was not irritating to intact skin but was to broken skin or to the eyes. Effects on the liver have been seen in humans exposed to DEP through dialysis equipment (BIBRA, 1989). Although phthalates are generally thought to have low potential for inducing dermatitis, with unsuccessful attempts to induce skin sensitization, contact dermatitis has been reported from medical products containing DEP (Oliwiecki *et al.*, 1991). Neuropathy has been associated with some phthalate acid esters. In a preliminary study of exposure of up to 250 workers to a vapor mixture of DEP, dibutylphthalate, and diethylhexylphthalate, no peripheral polyneuritis was observed in the population; however, no phthalates were detected in the blood before or after the phthalate exposure (ACGIH, 1991). When orally ingested at high doses, DMP is irritating to mucous membranes and the gastrointestinal tract and can cause central nervous system depression and hypotension (*Merck Index*, 1983; ACGIH, 1991).

CARCINOGENICITY

Experimental Animals

Groups of 15 male and 15 female rats (strain not specified) were fed 0%, 0.5%, 2.5%, or 5.0% DEP in a 2-year feed study. No effects were observed at levels of 0.5% or 2.5% DEP, with 5.0% resulting in a small but significant decrease in the growth rate of the rats without any effect on feed consumption (Food Research Laboratories, Inc., 1955). The DEP

study was considered by the EPA in their carcinogenicity assessment for lifetime exposure to DEP and was found inadequate as a design to measure carcinogenic effects.

While no adequate carcinogenicity studies were found for either DEP or DMP, the carcinogenic activity in rodents of agents structurally related to DEP or DMP has been extensively studied by the NTP. Related chemicals with equivocal or no evidence of carcinogenicity in rodents are: diallylphthalate (NTP, 1983, 1985), dimethylterephthalate (NCI, 1979a), phthalic anhydride (NCI, 1979b), and phthalamide (NCI, 1979c). Other related chemicals with positive evidence of carcinogenicity in rats and/or mice are: diethylhexylphthalate (NTP, 1982a), diethylhexyl adipate (NTP, 1982b), and butylbenzylphthalate (NTP, 1982c).

Humans

No information on human carcinogenicity was found in a search of the available literature.

Reproductive and Developmental Toxicity

Experimental Animals

In teratology studies, DEP was administered intraperitoneally on days 5, 10, and 15 of gestation to pregnant Sprague-Dawley rats at doses of 0.506, 1.012, and 1.686 mL/kg. The intermediate dose produced no resorption sites, but both high and low doses produced some resorptions (low dose = 3.6%, high dose = 44.4% of total implantations). All three doses produced decreased fetal weights. Skeletal malformations were also observed in dosed animals, with incidences up to 81%. No gross abnormalities were observed in any of the dose groups (Singh *et al.*, 1972).

In NTP teratology studies, DEP (at dietary doses of 0%, 0.25%, 2.5%, and 5.0%; NTP, 1988) or DMP (at doses of 0%, 0.2%, 1.0%, and 5.0%; NTP, 1989) were administered to pregnant CD rats during gestation days 6 through 15. In both studies, no treatment-related teratogenic effects were observed, even in doses producing maternal toxicity. In mice, dietary administration of DEP to males 7 days prior to mating and females 7 days prior to mating through 21 days after birth, affected paternal spermatogenesis as well as the live birth index (Lamb *et al.*, 1987). DEP administered dermally to pregnant mice (gestation days 1 to 17) resulted in some fetal musculoskeletal lesions (Tanaka *et al.*, 1987). DMP administered in feed to pregnant mice did not induce fetal abnormalities at maternally toxic doses (Plasterer *et al.*, 1985).

Phthalate esters (in a saturated Ringers solution) have caused growth retardation and malformations in the central nervous system of chick embryos. The effects appeared related to solubilities of esters in water (Lee *et al.*, 1974).

Humans

No information on human reproductive and developmental toxicity was found in a search of the available literature.

Genetic Toxicity

There are little published mutagenicity data on DEP and DMP; most of the available data are derived from bacterial mutagenicity tests. Kozumbo *et al.* (1982), Seed (1982), and Agarwal *et al.* (1985) reported small increases in the number of mutant colonies for strains TA100 and/or TA1535 treated with DMP (maximum doses ranged from 2,000 to 4,000 μg/plate) in the absence of S9 activation. In contrast, Zeiger *et al.* (1985) found no evidence of DMP-induced mutagenicity in several strains of *Salmonella*, including TA100 and TA1535, treated with up to 5,000 μg/plate with and without S9. Although each of these *Salmonella* tests had slight protocol variations, all appeared to have been conducted adequately. Therefore, errors in protocol or data analyses probably do not account for the discrepancies. Differing results among laboratories are not totally unexpected when tests involve chemicals that produce very weak mutagenic responses, particularly when these responses occur at concentrations that also produce significant toxicity.

In tests with mammalian cells, DMP (at concentrations greater than 1,000 μg/plate) was reported to induce sister chromatid exchanges but not chromosomal aberrations in Chinese hamster ovary cells treated *in vitro* in the presence of Aroclor 1254-induced rat liver S9 (Loveday *et al.*, 1990).

DEP was reported to be nonmutagenic in several strains of *Salmonella typhimurium*, with and without S9 activation (Omori, 1976; Florin *et al.*, 1980;

Blevins and Taylor, 1982; Zeiger *et al.*, 1985). Maximum doses tested in these studies reached 10,000 μg/plate. However, like DMP, positive responses in the *Salmonella* assay were reported at concentrations within the range tested in the studies that gave negative results. Seed (1982) reported weakly positive responses for DEP in the *Salmonella* assay (strain TA100) with and without S9, and Agarwal *et al.* (1985) found significant dose-related increases in revertant colonies in TA100 and TA1535 in the absence of S9. The mutagenic responses obtained with DEP in these laboratories were somewhat stronger than the responses observed after treatment of cells with DMP.

DEP was also tested for chromosomal effects in mammalian cells *in vitro*. It did not induce chromosomal aberrations in Chinese hamster lung fibroblasts treated in the absence of S9 activation (Ishidate and Odashima, 1977). In this assay, the maximum concentration of DEP tested was 250 μg/mL.

As an indirect mechanism of genotoxicity, there is limited evidence that DEP is a weak inducer of hepatic peroxisome proliferation (Moody and Reddy, 1978). No information was found on the peroxisome proliferating activity of DMP. Of concern for DMP is the cleavage of the diester and release of the aliphatic alcohol, methanol. While *in vitro* assays have shown that liver homogenate-associated esterases hydrolyzed DMP to the monoester, a nonmutagenic compound in the *Salmonella* assay, methanol can be further metabolized to formaldehyde, a mutagenic compound in the *Salmonella* assay (Kozumbo and Rubin, 1991).

In conclusion, the published data indicate that DMP and DEP may be weakly mutagenic in *Salmonella* strains TA100 and/or TA1535, which mutate via base-substitution, and that DMP may have potential for producing DNA damage in mammalian cells. However, because the *in vitro* data are sparse and no *in vivo* data are available for analysis, the mutagenic profile of these the phthalates must be considered incomplete.

STUDY RATIONALE

The phthalates, including DEP and DMP, are used extensively as solvents and plasticizers in industry and as components of cosmetic formulations. Phthalates can account for over 40 percent of the final composition of finished plastic products, and leaching of phthalates from the items may be a significant source of human exposure (Autian, 1980). DEP and DMP may be used, at no specific concentration limits, in many items in contact with food. This may include acrylic plastic articles, adhesive components, and resinous and polymeric coatings of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding of food (CFR 21, Part 58; Castle *et al.* 1988, 1989, 1990). In the workplace, the most likely routes of exposure are through inhalation and dermal absorption. Cosmetic products containing phthalates may be applied to or come in contact with skin, eyes, hair, nails, mucous membranes, and respiratory epithelium (CIRP, 1985). DEP and DMP both exhibit considerable dermal absorption in rats (Elsisi *et al.*, 1989). DEP, DMP, and other phthalate esters have become ubiquitous low- to moderate-level pollutants in the environment as a result of their widespread use.

Based on results of acute toxicity studies, DEP and DMP have been classified as practically nontoxic or relatively harmless. However, the subchronic and chronic toxicity of DEP or DMP have not been comprehensively evaluated. Previous NCI/NTP studies have examined the long-term effects of phthalates or phthalate-related compounds. The results of these studies have been both positive [di(2-ethylhexyl)phthalate (NTP, 1982a), diethylhexyl adipate (NTP, 1982b), and butylbenzyl phthalate (NTP, 1982c)] and negative [diallyl phthalate (NTP, 1983, 1985) and dimethyl terephthalate (NCI, 1979a)] for rodent carcinogenicity. Di(2-ethylhexyl)phthalate is nonmutagenic *in vitro*, and signal transduction, oncogene expression, and tumor promotion have all been suggested as alternative hypotheses to explain the hepatocarcinogenicity of di(2-ethylhexyl)-phthalate. While most reports suggest that DEP and DMP are at most weakly mutagenic, other reports have suggested DMP is clastogenic, possibly secondary to formaldehyde, a putative oxidative product of the DMP-metabolite methanol (Kozumbo *et al.*, 1982; Kozumbo and Rubin, 1991).

Based upon high exposure potential and lack of long-term toxicity or carcinogenicity information, DEP and DMP were nominated to the National Toxicology

Program by the EPA. Due to high exposure concentrations via cosmetic applications and to workplace exposure, the dermal route was chosen for these studies. This report summarizes findings of two separate evaluations: 2-year dermal studies of DEP in male and female F344/N rats and B6C3F$_1$ mice, and a series of special 1-year studies examining the potential of DEP or DMP as either tumor initiators or tumor promoters in an initiation/promotion skin model using male Swiss (CD-1®) mice.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Diethylphthalate

Diethylphthalate (DEP) was obtained from Tennessee Eastman Company (Kingsport, TN) in one lot (84117), which was used throughout the 4-week dermal studies in rats and mice, the 2-year dermal studies in rats and mice, and the 1-year dermal initiation/promotion study in male mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix H). Reports on analyses performed in support of the DEP studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a clear colorless liquid, was identified as DEP by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analyses, Karl Fischer water analysis, titration of free acid, ester titration, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for DEP. Karl Fischer water analysis indicated 0.083% ± 0.003% water. Free acid titration indicated less than 0.00006 mEq acid per gram of sample. Ester titration indicated a purity of 100.9% ± 0.3%. Thin-layer chromatography indicated one major spot. Gas chromatography indicated one major peak and no impurities with peak areas greater than 0.1% of the major peak. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that DEP was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. During the 4-week, 1-year, and 2-year studies, the bulk chemical was stored in amber glass bottles at room temperature until 12 December 1986 after which dose formulations were stored at 4° to 5° C. The stability of the bulk chemical was monitored periodically by the study laboratory using gas chromatography and free acid titration. No degradation of the bulk chemical was observed.

Dimethylphthalate

Dimethylphthalate (DMP) was obtained from Chemical Technical Industries (Orlando, FL) in one lot (C122883), which was used during the 1-year dermal initiation/promotion study in male mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory. Reports on analyses performed in support of the DMP study are on file at the NIEHS.

The chemical, a clear colorless liquid, was identified as DMP by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analyses, Karl Fischer water analysis, titration of free acid, ester titration, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for DMP. Karl Fischer water analysis indicated 0.039% ± 0.002% water. Free acid titration indicated 0.00060 ± 0.00004 mEq of acid per gram of sample. Ester titration indicated a purity of 99.2% ± 0.8%. Thin-layer chromatography indicated one major spot. Gas chromatography indicated one major peak, and no impurities with peak areas greater than 0.1% of the major peak. The overall purity was determined to be equal to or greater than 99%.

Stability studies were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that DMP was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. During the 1-year study, the bulk chemical was stored in 1-gallon amber glass bottles at 4° C. The stability of the bulk chemical was monitored periodically by the study laboratory using gas chromatography and ester titration. No degradation of the bulk chemical was observed.

7,12-Dimethylbenz(a)anthracene

7,12-Dimethylbenz(a)anthracene (DMBA) was obtained from the Eastman Kodak Company (Rochester, NY) in one lot (K-4) which was used during the 1-year initiation/promotion study in male mice. The lot was purified by the analytical chemistry laboratory and assigned lot number M111384.

The chemical, a light yellow powder, was identified as DMBA by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for DMBA. Karl Fischer water analysis indicated less than 0.4% water. Thin-layer chromatography indicated one major spot and one trace spot. Gas chromatography indicated one major peak with no impurities with peak areas greater than 0.1% of the major peak. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory with gas chromatography. These studies indicated that DMBA was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. In the 1-year study, the bulk chemical was stored in amber glass bottles at 4° C. The stability of the bulk chemical was monitored periodically by the study laboratory using ultraviolet spectroscopy and gas chromatography. No degradation of the bulk chemical was observed.

12-*O*-Tetradecanoylphorbol-13-acetate

12-*O*-Tetradecanoylphorbol-13-acetate (TPA) was obtained from Consolidated Midland Corporation (Brewster, NY) in one lot (031), from Pharmacia PL Biochemical (Milwaukee, WI) in three lots (UN2811, 411999, and OE511999), and from L.C. Services Corporation (Woburn, MA) in one lot (F-121). All five lots were used during the 1-year initiation/promotion study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory.

Each lot of the chemical was identified as TPA by nuclear magnetic resonance spectroscopy and mass spectrometry. The purity of the five lots was determined by thin-layer chromatography and high-performance liquid chromatography. Thin-layer chromatography indicated one major spot for all five lots, and one (lot 411999) or two (lot 031) trace impurities. High-performance liquid chromatography indicated one major peak in all five lots. In addition, high-performance liquid chromatography of lots 031 and UN2811 indicated seven or 11 trace impurities with peak areas that were approximately 3% of the major peak, respectively. High-performance liquid chromatography indicated between two and five trace impurities in lots 411999, OE511999, and F-121 with peak areas that were approximately 1% of the major peak. The overall purity was determined to be 97% for lots 031 and UN2811 and 99% for lots 411999, OE511999, and F-121.

The stability of the chemical was determined using high-performance liquid chromatography. There was no decomposition in samples exposed to air and light at ambient temperature for up to 6 days. The study laboratory stored the chemical in sealed vials at −20° C.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Diethylphthalate

DEP was applied neat in the 4-week rat and mouse studies, 1-year mouse study, and 2-year rat study. In the 2-year mouse study, the dose formulations were prepared by mixing DEP and acetone to give the required concentration (Table H1). Dose formulations were discarded 3 weeks after the date of preparation.

Dose formulation stability studies were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the DEP dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark, and for at least 3 hours when exposed to light and air. Periodic analyses of the dose formulations of DEP were conducted by the study laboratory and analytical chemistry laboratory using reverse-phase high-performance liquid chromatography. During the 2-year mouse study, the dose formulations were analyzed at least once every 8 weeks (Table H2) and 91% (52/57) of the dose formulations analyzed were within 10% of the target concentrations. No formulation was greater than 21% from the target concentration. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table H4).

Dimethylphthalate
DMP was applied neat in the 1-year mouse study.

7,12-Dimethylbenz(a)anthracene
During the 1-year mouse study, the dose formulation was prepared by dissolving DMBA in acetone, with formulation analysis conducted prior to the beginning of the study (Table H3). Stability analyses of the dose formulations were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the dose formulations was confirmed for up to 3 weeks at room temperature when stored in the dark, and for less than 3 hours when exposed to light and air. Confirmatory analysis of the dose formulation of DMBA was conducted by the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy. The dose formulation was found to be within 10% of the target concentration by both laboratories (Tables H3 and H4).

12-*O*-Tetradecanoylphorbol-13-acetate
For the 1-year mouse study, dose formulations were prepared every 2 weeks by dissolving TPA in acetone. The dose formulations were refrigerated in amber glass bottles and were discarded 3 weeks after the date of preparation. Stability analyses of the acetone solutions were conducted by the analytical chemistry laboratory using high-performance liquid chromatography. Stability of the formulation was established for at least 3 weeks when stored at 4° C in amber glass bottles. Periodic analyses of the dose formulations of TPA were conducted by the study laboratory using high-performance liquid chromatography. In the study, only 54% (7/13) of the formulations analyzed were within 10% of the target concentration, but no formulation was greater than 26% from the target concentration (Table H3). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H4).

4-Week Studies
The 4-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to DEP and to determine the appropriate dose levels to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). Upon receipt, rats and mice were approximately 29 days old. The animals were quarantined for 13 days before exposure began. At this time, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Groups of 10 male and 10 female rats were administered 0, 37.5, 75, 150, or 300 μL DEP; groups of 10 male and 10 female mice were administered 0, 12.5, 25, 50, or 100 μL DEP. Doses were applied to clipped interscapular skin five times per week. Clinical findings were recorded weekly. Animals were weighed initially and weekly thereafter. Further details of study design and animal maintenance are summarized in Table 2.

The right kidney, liver, right testis, and thymus of all surviving animals were weighed. A necropsy was performed on all animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all animals. Table 2 lists the tissues and organs routinely examined.

2-Year Studies
Study Design
Groups of 60 male and 60 female rats were administered 0, 100, or 300 μL DEP. An initial 2-year study in mice at doses of 0, 35, and 100 μL (applied neat) was aborted due to marked body weight gain reductions. In a restart, groups of 60 male and 60 female mice were administered 0, 7.5, 15, or 30 μL DEP dissolved in acetone for a total application volume of 100 μL of solution. Doses were applied to clipped interscapular skin five times per week for 104 weeks (rats) or for 104 to 105 weeks (mice). Animals were clipped weekly or as needed. Ten male and 10 female rats and mice from each group were designated for interim evaluations after 15 months of chemical administration.

Source and Specification of Animals
Male and female F344/N rats were obtained from Frederick Cancer Research Facility (Frederick, MD). Male and female B6C3F$_1$ mice were obtained from Taconic Farms, Inc. (Germantown, NY). Animals were quarantined for 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. Serology samples were collected for viral screening. 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 J).

Animal Maintenance

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

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded initially and monthly thereafter. Animals were weighed at study initiation, weekly for the first 13 weeks, and monthly thereafter. At the 15-month interim evaluations blood for hematology and clinical chemistry (rats only) was collected from the retroorbital sinus of animals designated for clinical pathology studies. Automated determinations were performed using a Coulter® S+IV. The clinical pathology parameters measured are listed in Table 2. The brain, right kidney, and liver were weighed at the 15-month interim evaluations.

A necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Complete histopathologic examinations were performed on all control and high-dose animals at the 15-month interim evaluation and on all animals at 2 years. Tissues examined are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic 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. A quality assessment pathologist reviewed the cecum, forestomach, and mesenteric lymph nodes of male and female rats; the colon and liver of male rats; the clitoral gland of female rats; the liver of male and female mice; and the uterus and thyroid gland of female mice for accuracy and consistency of lesion diagnosis. An independent review of the proliferative lesions of the pituitary gland and testes of male rats was conducted to verify incidence values.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the potential target tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologist existed. Representative examples of potential chemical-related lesions, including neoplasms of the forestomach, large intestine, mesenteric lymph node, and clitoral gland from rats and the liver, uterus, thyroid gland, and forestomach from mice, and examples of disagreements in diagnosis between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair 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. Thus, the final diagnoses represent a consensus of contractor pathologists 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 pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

1-Year Initiation/ Promotion Study

The 1-year study was conducted to evaluate the potential of dermally applied DEP or DMP to initiate tumorigenesis when followed by a strong promoter or to promote tumorigenesis following a known initiator. Initiators and promoters, as operationally defined in studies of this kind, have minimal

activity as complete chemical carcinogens. However, exposure to an initiator (DMBA) followed subsequently by a tumor promoter (TPA) results in marked enhancement in carcinogenicity.

Male Swiss (CD-1®) mice were obtained from Charles River Breeding Laboratories (Kingston, NY). Upon receipt, the mice were 5 weeks old. The animals were quarantined for 12 days before dosing began. At the end of quarantine, five mice were evaluated for evidence of disease. The health of the animals was monitored during the study according to the NTP Sentinel Animal Program (Appendix J). Animals were approximately 7 weeks old at the beginning of the study.

Groups of 50 Swiss (CD-1®) male mice were dermally administered various initiation/promotion treatments. Chemicals were applied to the clipped interscapular skin. Animals were clipped weekly or as needed. All chemicals used as initiators were applied once during the first week of treatment. Promoters were generally applied three or five times per week from week 2 through the end of the study. Because of severe skin irritation in groups with acetone or TPA as promotion treatments, application of these chemicals was suspended at week 8 and decreased to two times per week when application resumed at week 10. All doses were applied at a volume of 0.1 mL. Mice in the vehicle control group received one dose of acetone as an initiator, followed by acetone as a promoter three times per week for 8 weeks, and twice per week for the remaining 44 weeks (Table 1). Initiators (acetone, DMBA, DEP, or DMP) were generally applied once during week 1 of the study. Promoters (acetone, TPA, DEP, or DMP) were generally applied three times per week for the first 8 weeks of the study and two times per week for the remaining 44 weeks.

Mice were housed individually with feed and water available *ad libitum*. Cages and racks were rotated every 2 weeks. Animals were observed twice daily. Clinical findings and body weights were recorded weekly for the first 13 weeks and monthly thereafter. Further details of animal maintenance are given in Table 2.

A complete necropsy was performed on all animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on animals from the acetone/DMP and acetone/acetone groups. Table 2 lists the tissues and organs routinely examined.

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 were censored from the survival analyses if they were found dead of other than natural causes or if they were missing; 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 as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number 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., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical

TABLE 1
Design of the 1-Year Dermal Initiation/Promotion Study of Diethylphthalate and Dimethylphthalate in Male Swiss (CD-1®) Mice[a]

Treatment[b]		
Initiator[c]	Promoter[d]	Test Group
Acetone	Acetone[e]	Vehicle Control
DMBA	TPA[f]	Initiation/Promotion Control
DMBA	Acetone	DMBA Initiation Control
DEP	Acetone	DEP Initiation Control
DMP	Acetone	DMP Initiation Control
DEP	TPA	DEP Initiation
DMP	TPA	DMP Initiation
Acetone	TPA	TPA Promotion Control
Acetone	DEP[g]	DEP Promotion Control
Acetone	DMP[g]	DMP Promotion Control
DMBA	DEP	DEP Promotion
DMBA	DMP	DMP Promotion

[a] 50 mice per treatment group
[b] DMBA = 7,12-dimethylbenz(a)anthracene, TPA = 12-*O*-tetradecanoylphorbol-13-acetate, DEP = diethylphthalate, and DMP = dimethylphthalate
[c] Initiators were applied once during week 1 of the study, in a volume of 0.1 mL; DEP and DMP applied neat, DMBA applied in solution with acetone, 0.5 mg/mL
[d] Promoters were applied in a volume of 0.1 mL
[e] Acetone promotion: 3 times per week for 8 weeks, then 2 times per week for 44 weeks
[f] TPA promotion: 0.05 mg/mL solution, 3 times per week for 8 weeks, then a 0.025 mg/mL solution, 2 times per week for 44 weeks
[g] DEP and DMP promotion: 5 times per week for 52 weeks

method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test

(Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluations, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

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 have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology and clinical chemistry data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response 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-response trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 1-year 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, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. 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 so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicities of DMP and DEP were assessed by testing the ability of the chemicals to induce mutations in various strains of *Salmonella typhimurium* and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of DMP and DEP 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 structure of the chemical and its responses 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 electrophilic theory of chemical carcinogenesis and the somatic mutation theory (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 do not correlate 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 the NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complimentarity 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 is not yet defined.

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies of Diethylphthalate/Dimethylphthalate

4-Week Studies	2-Year Studies	1-Year Study
Study Laboratory Hazleton Laboratories America, Inc. (Rockville, MD)	Hazleton Laboratories America, Inc. (Rockville, MD)	Hazleton Laboratories America, Inc. (Rockville, MD)
Strain and Species Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Mice: Swiss (CD-1®)
Animal Source Simonsen Laboratories (Gilroy, CA)	Rats: Frederick Cancer Research Facility (Frederick, MD) Mice: Taconic Farms, Inc. (Germantown, NY)	Charles River Breeding Laboratories (Kingston, NY)
Size of Study Groups 10 males and 10 females	60 males and 60 females	50 males
Time Held Before Studies 13 days	14 days	12 days
Average Age When Studies Began 6 weeks	6 weeks	7 weeks
Date of First Dose 5 September 1984	Rats: 6 February 1985 Mice: 23 December 1986	29 July 1985
Duration of Dosing 32-33 days	Rats: 104 weeks Mice: 104-105 weeks	55 weeks
Date of Last Dose 7-8 October 1984	Rats: 2 February 1987 Mice: 14-22 December 1988	11 August 1986
Method of Sacrifice Carbon dioxide asphyxiation	Same as 4-week studies	Same as 4-week studies
Necropsy Dates 7-8 October 1984	Rats: 9-10 February 1987 Mice: 21-29 December 1988	19-27 August 1986
Average Age at Necropsy 11 weeks	111 weeks	62 weeks
Method of Animal Distribution Animals were randomly assigned to groups by a computer generated randomization procedure	Animals were randomly assigned to groups by a computer generated randomization procedure	Randomly assigned to groups

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies of Diethylphthalate/Dimethylphthalate (continued)

4-Week Studies	2-Year Studies	1-Year Study
Animals per Cage		
1	1	1
Method of Identification		
Toe clip	Toe clip	Toe clip
Diet		
NIH-07 open formula meal (Zeigler Brothers, Gardners, PA), available *ad libitum*	Same as 4-week studies	Same as 4-week studies
Feeders		
Stainless-steel hopper-type (Lab Products, Inc., Garfield, NJ)	Same as 4-week studies	Same as 4-week studies
Water		
Automatic watering system; available *ad libitum*	Same as 4-week studies	Same as 4-week studies
Cages		
Polycarbonate (Lab Products Inc., Garfield, NJ); changed once a week, rotated every other week	Same as 4-week studies	Same as 4-week studies
Bedding		
BetaChips® (Northeastern Products Corp., Warrensburg, NY)	BetaChips® (Northeastern Products Corp., Warrensburg, NY); on 19 April 1988 changed to Sani-Chips (P.J. Murphy, Forest Products Corp., Montville, NJ) for mice	Same as 4-week studies
Cage Filters		
Nonwoven polyester (Snow Filtration Co. Cincinnati, OH)	Same as 4-week studies	Same as 4-week studies
Racks		
Stainless steel (Lab Products Inc., Garfield, NJ); changed every other week	Same as 4-week studies	Same as 4-week studies
Animal Room Environment		
Rats: Temperature: 22°-24° C Relative humidity: 32%-58% Fluorescent light: 12 hours/day Room air changes: minimum of 12 changes/hour Mice: Temperature: 23°-24° C Relative humidity: 28%-74% Fluorescent light: 12 hours/day Room air changes: minimum of 12 changes/hour	Rats: Temperature: 20°-25° C Relative humidity: 28%-74% Fluorescent light: 12 hours/day Room air changes: more than 12 changes/hour Mice: Temperature: 19°-25° C Relative humidity: 23%-92% Fluorescent light: 12 hours/day Room air changes: more than 12 changes/hour	Temperature: 19°-25° C Relative humidity: 32%-73% Fluorescent light: 12 hours/day Room air changes: more than 12 changes/hour

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies of Diethylphthalate/Dimethylphthalate (continued)

4-Week Studies	2-Year Studies	1-Year Study
Doses		
Rats: 0, 37.5, 75, 150, or 300 μL DEP applied to clipped interscapular skin Mice: 0, 12.5, 25, 50, or 100 μL DEP applied to clipped interscapular skin	Rats: 0, 100, or 300 μL DEP applied neat to clipped interscapular skin Mice: 0, 7.5, 15, or 30 μL DEP dissolved in acetone for a total volume of 100 μL of solution applied to clipped interscapular skin	See Table 1
Type and Frequency of Observation		
Animals observed twice daily; clinical findings, and weights recorded initially and weekly thereafter.	Animals observed twice daily; clinical findings recorded initially and then monthly; body weights recorded initially, weekly for the first 13 weeks and monthly thereafter.	Animals observed twice daily; clinical findings and body weights recorded weekly for the first 13 weeks and monthly thereafter.
Necropsy		
Necropsy performed on all animals. Organs weighed were right kidney, liver, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were brain, right kidney, and liver at the 15-month interim evaluations.	Necropsy performed on all animals.
Clinical Pathology		
None	Blood samples were collected from the retroorbital sinus of rats and mice at the 15-month interim evaluations. ***Hematology:*** Hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leukocyte count and differential, and nucleated erythrocytes ***Clinical chemistry (rats only):*** urea nitrogen, creatinine, alkaline phosphatase, sorbitol dehydrogenase	None

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies of Diethylphthalate/Dimethylphthalate (continued)

4-Week Studies	2-Year Studies	1-Year Study
Histopathology		
Complete histopathologic examinations were performed on all animals. In addition to gross lesions and tissue masses, tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (colon, cecum, rectum), liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nose, ovary, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, skin (site of application, control, and other), small intestine (duodenum, jejunum, ileum), spleen, sternum, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all control and high-dose animals at the 15-month interim evaluation and on all animals at 2 years. In addition to gross lesions and tissue masses, tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (colon, cecum, rectum), liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nose, ovary, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, skin (site of application, control, and other), small intestine (duodenum, jejunum, ileum), spleen, sternum, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. For all other groups, gross lesions and tissue masses were examined.	Complete histopathologic examinations were performed on all animals from the acetone/DMP and acetone/acetone groups. In addition to gross lesions and tissue masses, tissues examined included: adrenal gland, brain, esophagus, gallbladder, heart, kidney, large intestine (colon, cecum, rectum), liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nose, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicles, skin (site of application, control and other), small intestine (duodenum, jejunum, ileum), spleen, sternum, stomach, testis, thymus, thyroid gland, trachea, and urinary bladder. For all other groups, in addition to gross lesions and tissue masses, tissues examined included lungs and skin (site of application, control, and other).

RESULTS

4-Week Study of Diethylphthalate in F344/N Rats

All male and female rats survived to the end of the study (Table 3). Final mean body weights of male and female rats were similar to those of controls. Feed consumption by dosed rats was similar to that by controls.

There were no clinical signs of toxicity, including no evidence of dermatotoxicity, related to chemical administration. Relative liver weights were greater than those of controls in 300 μL males and in 150 and 300 μL females (Table F1). Relative kidney weights were greater than those of controls in 150 and 300 μL males and in 150 μL females (Table F1).

Doses of 0, 100, or 300 μL per day were recommended for the 2-year rat study on the basis of organ weights. 300 μL was considered a reasonable maximum volume for rat studies involving daily skin application.

TABLE 3
Survival and Body Weights of Rats in the 4-Week Dermal Study of Diethylphthalate

Dose (μL)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	116 ± 3	220 ± 5	103 ± 3	
37.5	10/10	114 ± 4	212 ± 6	98 ± 3	97
75	10/10	114 ± 3	215 ± 6	101 ± 4	98
150	10/10	114 ± 3	211 ± 4	97 ± 3	96
300	10/10	115 ± 3	209 ± 5	94 ± 4	95
Female					
0	10/10	93 ± 2	139 ± 3	47 ± 2	
37.5	10/10	91 ± 2	137 ± 2	46 ± 1	98
75	10/10	95 ± 2	139 ± 3	45 ± 3	100
150	10/10	93 ± 1	137 ± 2	44 ± 3	99
300	10/10	92 ± 2	135 ± 4	44 ± 3	97

[a] Number of animals surviving at 4 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Williams' or Dunnett's test.

2-YEAR STUDY OF DIETHYLPHTHALATE IN F344/N RATS

Based upon the results of the 4-week study, groups of 60 male and 60 female F344/N rats were administered diethylphthalate (DEP) at doses of 0, 100, or 300 μL, 5 days per week for 103 weeks. Up to 10 rats per group were evaluated after 15 months of dosing.

Survival

Estimates of the survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier curves in Figure 1. Prior to the 15-month interim evaluation, the average survival for dosed rats was similar to that of controls (95% or greater) with the majority of males and females designated for interim evaluation (9 to 10 per group) surviving to the 15-month evaluation. However, after 15 months, mortality was significantly increased in all groups regardless of treatment (particularly after week 73 in males and after week 89 in females). Thus, 2-year survival was significantly reduced in all groups, regardless of treatment (Table 4). Survival of male and female rats administered DEP was similar to controls, although a dose-related decrease was suggested throughout the second year in female rats (Figure 1).

Body Weights and Clinical Findings

Body weights of male and female control rats reflected mortality findings, with normal body weight gains through week 73 in male rats and through the majority of the study in female rats (Figure 2 and Tables 5 and 6). Throughout the study, DEP-dosed male rats experienced small to moderate, dose-related depressions in mean body weights. Male rats weighed approximately 2% to 5% less than controls in the 100 μL group, and 4% to 9% less than controls in the 300 μL group. The final mean body weights in the male rats represented only 5 or 6 animals but were considerably lower for all groups, with the largest decrease in the 300 μL group (Table 5). Final mean body weights of females were similar to that of controls (Table 6).

Male and female rats (irrespective of treatment group, males more frequently than females) followed a rapid course of weight loss, loss of appetite, hypoactivity, emaciation, inactivity, and general deterioration of health (requiring moribund sacrifice). Otherwise, no adverse clinical signs were observed. In particular, no gross signs of significant dermatotoxicity at the site of application were apparent. However, dosed rats experienced an increased incidence of slight crusting of the skin at the site of application. One papillomatous growth was observed in one control and one 100 μL male, and one carcinomatous growth in a 300 μL female.

Organ weights or organ weight to body weight ratios of dosed rats evaluated at 15 months were not significantly different from controls (Table F2).

Hematology and Clinical Chemistry

At the 15-month interim evaluation, hematocrit values, hemoglobin concentrations, and erythrocyte counts in the 300 μL female rats were significantly higher than those in controls (Table G1). These differences were minimal and not consistent between sexes, but would be consistent with hemoconcentrations resulting from dehydration. Other differences were minor, sporadic, and not considered treatment related.

TABLE 4
Survival of Rats in the 2-Year Dermal Study of Diethylphthalate

Dose (μL)	0	100	300
Male			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	9
Moribund	31	38	26
Natural deaths	15	6	19
Animals surviving to study termination	4[e]	6	6
Percent probability of survival at end of study[b]	8	12	12
Mean survival (days)[c]	585	597	594
Survival analysis[d]	P=0.640N	P=0.313N	P=0.545N
Female			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	9	10	10
Moribund	12	12	17
Natural deaths	9	10	10
Animals surviving to study termination	30	28	23[f]
Percent probability of survival at end of study	59	56	47
Mean survival (days)	648	640	622
Survival analysis	P=0.162	P=0.835	P=0.202

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

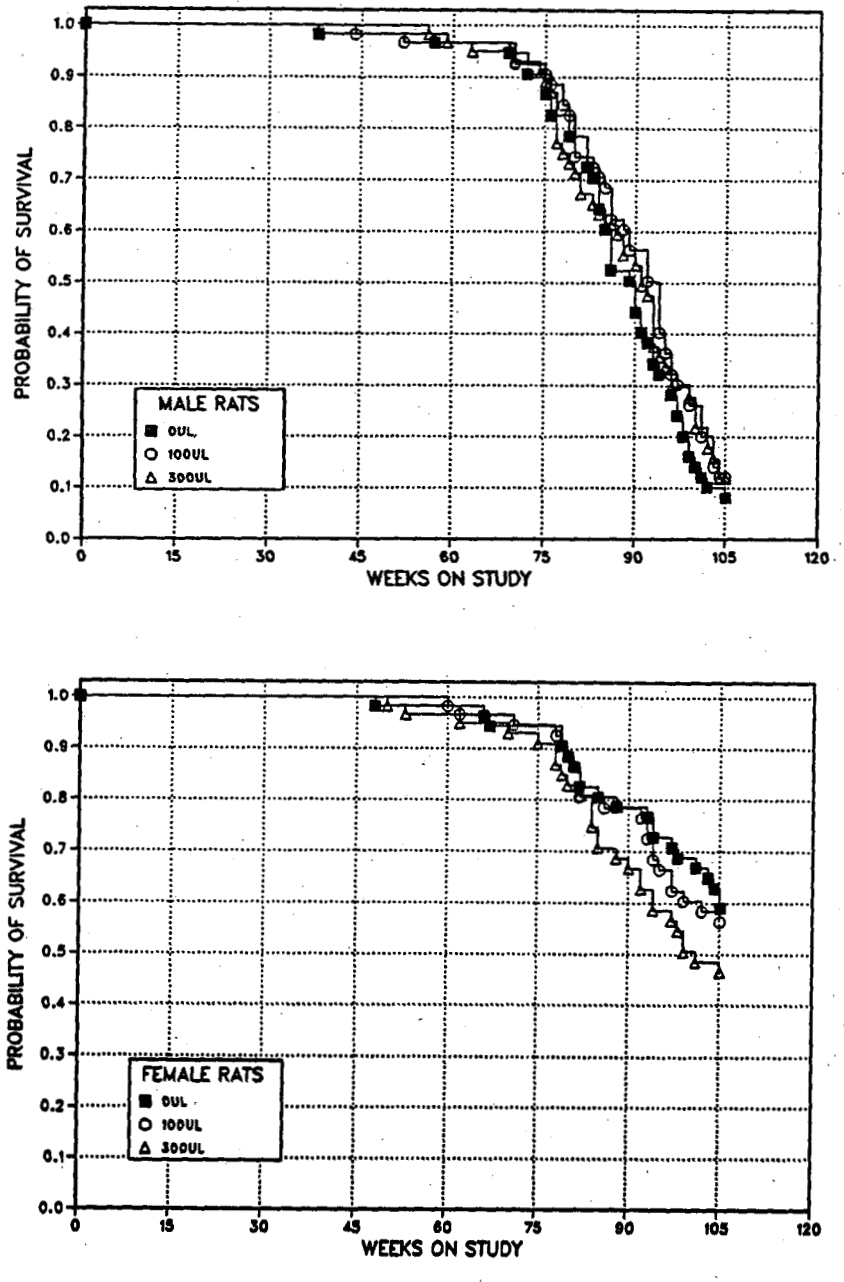


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Diethylphthalate Dermally for 2 Years

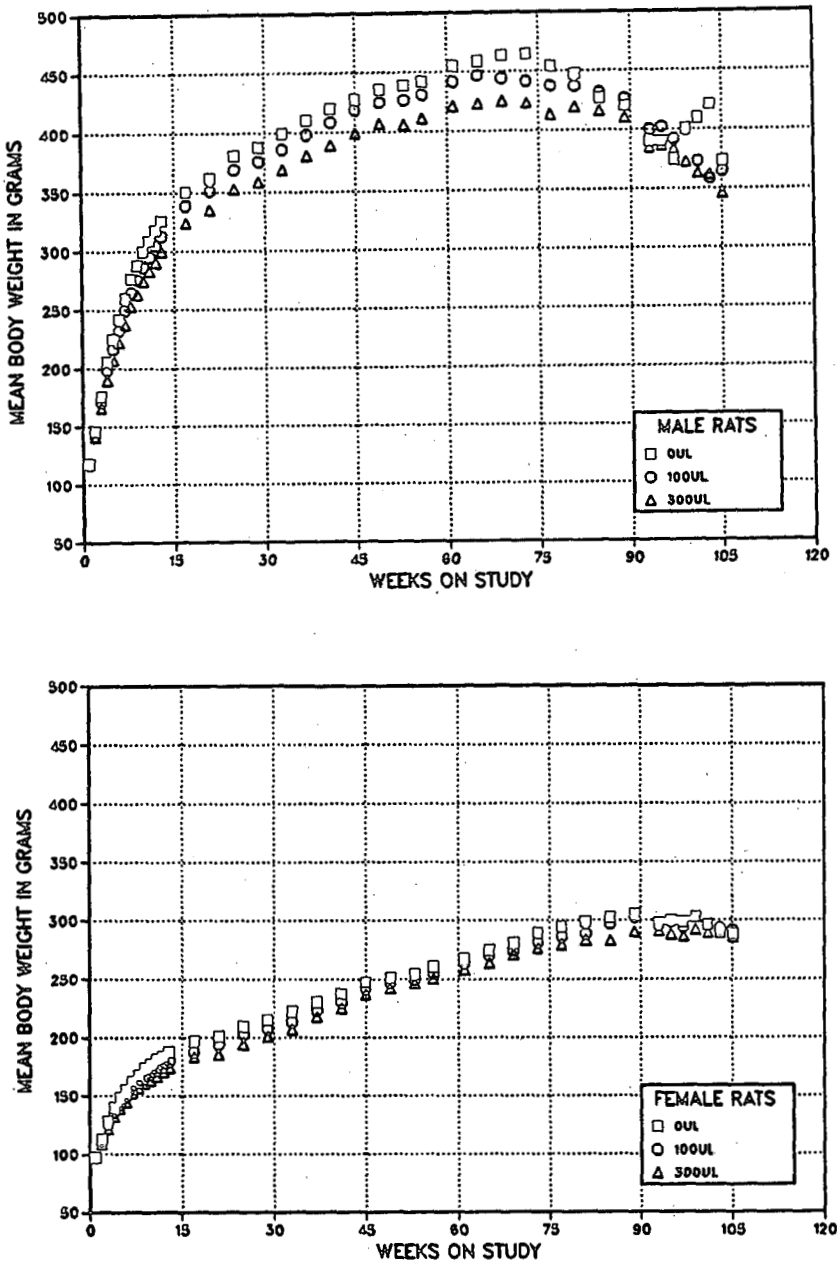


FIGURE 2
Growth Curves for Male and Female Rats Administered Diethylphthalate Dermally for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Diethylphthalate

Weeks on Study	0 µL		100 µL			300 µL		
	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	118	50	117	100	50	118	100	51
2	146	50	143	98	50	140	96	51
3	177	50	172	97	50	166	94	51
4	206	50	199	97	50	190	92	51
5	225	50	217	97	50	207	92	51
6	242	50	232	96	50	222	92	51
7	261	50	250	96	50	238	91	51
8	277	50	265	96	50	254	92	51
9	289	50	276	95	50	264	92	51
10	300	50	287	96	50	275	92	51
11	309	50	296	96	50	284	92	51
12	318	50	305	96	50	291	91	51
13	327	50	314	96	50	300	92	51
17	351	50	339	97	50	325	93	51
21	363	50	352	97	50	336	93	51
25	381	50	369	97	50	354	93	51
29	389	50	376	97	50	359	92	51
33	399	50	386	97	50	369	92	51
37	411	50	399	97	50	381	93	51
41	421	49	409	97	50	389	93	51
45	427	49	419	98	49	399	93	51
49	436	49	425	98	49	407	93	51
53	440	49	427	97	48	407	92	51
56	444	49	431	97	48	412	93	50
61	456	48	442	97	48	422	93	49
65	460	48	447	97	48	424	92	48
69	464	48	444	96	48	425	92	48
73	465	45	441	95	46	423	91	47
77	454	41	437	96	44	413	91	44
81	447	39	437	98	37	419	94	36
85	427	32	432	101	35	416	98	32
89	420	26	427	102	30	411	98	28
93	390	19	400	103	25	385	99	24
95	390	16	402	103	20	387	99	18
97	374	14	392	105	16	383	103	15
99	400	9	399	100	14	373	93	15
101	410	7	373	91	13	364	89	11
103	421	5	358	85	10	361	86	9
105	373	5	365	98	6	346	93	6
Mean for weeks								
1-13	246		236	96		227	92	
14-52	398		386	97		369	93	
53-105	426		415	97		398	93	

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Diethylphthalate

Weeks on Study	0 μL		100 μL			300 μL		
	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	97	51	97	99	50	98	101	50
2	114	51	110	97	50	109	96	50
3	128	51	126	98	50	121	95	50
4	140	51	136	97	50	132	94	50
5	148	51	143	96	50	139	94	50
6	156	51	148	95	50	145	93	50
7	162	51	156	96	50	152	94	50
8	167	51	161	96	50	156	93	50
9	173	51	166	96	50	161	93	50
10	177	51	169	95	50	163	92	50
11	181	51	172	95	50	167	92	50
12	184	51	175	96	50	170	93	50
13	187	51	180	96	50	174	93	50
17	197	51	188	96	50	183	93	50
21	201	51	195	97	50	186	93	50
25	209	51	203	97	50	194	93	50
29	214	51	207	97	50	200	94	50
33	222	51	213	96	50	207	93	50
37	230	51	223	97	50	218	95	50
41	238	51	230	97	50	225	95	50
45	248	51	242	98	50	237	96	50
49	251	50	248	99	50	242	96	50
53	255	50	249	98	50	246	97	49
56	261	50	255	98	50	250	96	48
61	268	50	263	98	49	258	96	48
65	275	50	270	98	48	263	96	47
69	281	48	275	98	48	271	97	47
73	289	48	281	97	47	277	96	46
77	294	48	286	97	47	279	95	45
81	299	45	288	97	44	283	95	41
85	303	42	297	98	40	283	93	37
89	305	40	303	99	39	290	95	34
93	297	40	295	99	38	291	98	31
95	300	37	298	99	33	288	96	29
97	299	37	294	99	33	286	96	29
99	303	35	302	100	30	292	96	26
101	296	35	296	100	30	289	98	25
103	291	34	293	101	29	289	99	24
105	288	32	291	101	29	286	99	24
Mean for weeks								
1-13	155		149	96		145	94	
14-52	223		217	97		210	94	
53-105	288		284	99		278	97	

Pathology Findings

This section describes the statistically significant and biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin, pituitary gland, mammary gland, and testes. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, the statistical analyses of the primary neoplasms that occurred with an incidence of at least 5% in at least one group, and the historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendix A for males and Appendix B for females.

In this study, no statistically significant treatment-related positive trends were identified for neoplasms in male rats. The statistically significant increases noted in female rats appeared to be spurious and within historical control values. The combined incidence of benign or malignant neoplasms in all organs in female rats was decreased in dosed groups. No neoplasms or nonneoplastic lesions occurred with significant incidence in animals at the interim evaluation.

Skin, Site of Application: Skin neoplasms were not observed in female rats and were only rarely observed in male rats (Tables A1 and B1). There were no significant dose-related trends in the incidence of neoplasms at the site of application (Tables A3 and B3). A treatment-related, increased incidence of minimal to mild epidermal acanthosis was observed in dosed males and females at the site of application (Tables 7, A5, and B5). This lesion was considered to be a subtle adaptive response to local irritation. In a few animals, minimal hyperkeratosis was associated with the acanthotic lesions. Acanthosis was also detected in male rats at the 15-month interim evaluation (Tables 7, A5, and B5).

TABLE 7
Incidences of Skin Lesions of Rats in the 2-Year Dermal Study of Diethylphthalate

Dose (μL)	0	100	300
15-Month Interim Evaluation			
Male			
Skin, site of application[a]	10	5	9
Acanthosis[b]	0	5** (1.0)[c]	6** (1.0)
Female			
Skin, site of application	–[d]	–	–
Acanthosis	–	–	–
2-Year Study			
Male			
Skin, site of application	50	50	51
Acanthosis	2 (1.5)	5 (1.4)	21** (1.1)
Female			
Skin, site of application	50	49	50
Acanthosis	8 (1.4)	18* (1.1)	23** (1.1)

* Significantly different (P≤0.05) from the control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
** P≤0.01
[a] Number of animals with skin examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate
[d] Skin not examined microscopically in this group

Pituitary Gland: Adenomas of the pars distalis of the pituitary gland occurred at an unusually high incidence in all groups, including the controls (male: 39/44, 41/49, 41/49; female: 38/50, 33/49, 33/48; Tables A1 and B1). Historical control values for F344/N rats in feed studies are considerably lower (male feed controls: 29%; range 12%-60%; female feed controls, 54%; range 30%-74%; Tables A4a and B4a). The higher incidence and early onset of this neoplasm observed in all groups of male rats was likely contributory to the poor survival of male rats in this study. The incidence of pituitary gland carcinomas at this site was unaffected by treatment.

Mammary Gland: A significant decrease in the incidence of fibroadenomas of the mammary gland occurred in dosed female rats and followed a negative trend (21/50, 12/48, 7/50; Table B3). The biological significance of this decrease is uncertain since neither the incidences of hyperplasia (9/50, 9/48, 9/50; Table B5) nor other mammary gland neoplasms (adenomas or carcinomas) were affected by treatment. The incidence of fibroadenomas in the historical control database was similar to the incidence in controls in this study (female feed controls: 38.6%; range 8%-58%; Table B4b).

Other: The incidence of mononuclear cell leukemia in control and dosed male rats (9/50, 12/50, 13/51; Table A3) was distinctly lower than the historical incidence of mononuclear cell leukemia: (male feed controls: 49%; range 32%-62%; Table A4b). This may be attributable to the shortened lifespan of male rats. Similarly, the incidence of testicular adenomas in both control and dosed male rats (4/50, 3/50, 9/50; Table A1) was also markedly lower than the historical control incidence (feed controls: 90%; range 74%-98%; Table A4c). Spontaneous pituitary adenomas of rats have been shown to elevate plasma prolactin concentrations, hormonal effects which may alter the development of testicular proliferative lesions (van Nesselrooij *et al.*, 1992).

In the liver, the incidence of fatty degeneration was notably decreased in both male (26/50, 8/50, 4/51; Table A5) and female (23/50, 11/50, 3/50; Table B5) rats. These decreased incidences were dose-related and may be attributable to the hypolipidemic action of this chemical.

4-Week Study of Diethylphthalate in B6C3F$_1$ Mice

All male mice and all but one of the female (control) mice survived to the end of the study (Table 8). Final mean body weights of male mice were similar to controls. Final mean body weights of dosed female mice were 5% to 7% greater than that of controls. Feed consumption by dosed mice was similar to that by controls.

There were no clinical signs of toxicity, including no evidence of dermatotoxicity, related to chemical administration. Absolute and relative liver weights of 25 and 100 μL female mice were greater than those of controls (Table F3).

Based on the 4-week study results, doses of 0, 35, and 100 μL DEP were recommended for the 2-year mouse studies. A chronic study in male and female B6C3F$_1$ mice at 0, 35, and 100 μL (applied neat, once per day, 5 days per week) was started and subsequently stopped after 32 weeks when significant body weight differences were noted in dosed animals (35 μL males and females, 12% and 10% lower than controls; 100 μL males and females, 19% lower than controls). Based on these body weight differences, doses of 0, 7.5, 15, and 30 μL in 100 μL acetone were chosen for the restart of the 2-year mouse study.

TABLE 8
Survival and Body Weights of Mice in the 4-Week Dermal Study of Diethylphthalate

Dose (μL)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	20.6 ± 0.4	26.5 ± 0.5	5.9 ± 0.4	
12.5	10/10	21.1 ± 0.5	26.2 ± 0.5	5.2 ± 0.7	99
25	10/10	21.4 ± 0.4	25.7 ± 0.5	4.3 ± 0.6	97
50	10/10	21.1 ± 0.5	26.5 ± 0.5	5.5 ± 0.5	100
100	10/10	21.2 ± 0.6	26.0 ± 0.7	4.8 ± 0.3	98
Female					
0	9/10[c]	15.9 ± 0.3	21.0 ± 0.5	5.3 ± 0.5	
12.5	10/10	16.0 ± 0.2	22.1 ± 0.3	6.1 ± 0.4	105
25	10/10	16.5 ± 0.2	22.3 ± 0.3*	5.9 ± 0.2	106
50	10/10	16.4 ± 0.2	22.4 ± 0.3*	6.0 ± 0.3	107
100	10/10	16.4 ± 0.2	22.3 ± 0.3*	5.9 ± 0.3	106

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test.
[a] Number of animals surviving at 4 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 3

2-Year Study of Diethylphthalate in B6C3F$_1$ Mice

Based upon the results of the 4-week study, groups of 60 male and 60 female B6C3F$_1$ mice were administered diethylphthalate (DEP) at doses of 0, 7.5, 15, or 30 μL in 100 μL acetone, 5 days per week for 103 weeks. Up to 10 mice per group were evaluated after 15 months of dosing.

Survival

Estimates of the survival probabilities for male and female mice are shown in Table 9 and in the Kaplan-Meier curves in Figure 3. Survival of dosed mice at the 15-month interim evaluation and after 2 years was similar to that of the controls.

Body Weights and Clinical Findings

The mean body weights of male and female mice administered DEP were similar to the controls throughout the study (Tables 10 and 11 and Figure 4).

No clinical signs of toxicity were observed in mice, including no gross evidence of dermatotoxicity. The only notable clinical observation resulting from exposure to DEP was an increased incidence of scaly skin at the site of application in 48% of the males and 70% of the females in the 30 μL groups. Feed consumption by male and female mice was similar to or up to 13% greater than that by controls.

Minor increases in relative kidney weights were observed in 15 and 30 μL female mice at the 15-month interim evaluation (Table F4).

Hematology

Only minor, sporadic hematology differences were observed (Table G2). None were considered treatment related.

TABLE 9
Survival of Mice in the 2-Year Dermal Study of Diethylphthalate

Dose (μL)	0	7.5	15	30
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	0	1	0	0
Missing[a]	0	1	0	0
Moribund	2	3	2	1
Natural deaths	5	4	2	6
Animals surviving to study termination	43	41	46	43
Percent probability of survival at end of study[b]	86	86	92	86
Mean survival (days)[c]	668	643	680	671
Survival analysis[d]	P=0.980N	P=0.863	P=0.486N	P=1.000N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	9	10	10
Natural deaths	5	8	7	5
Moribund kills	4	5	5	8
Accidental deaths[a]	0	0	0	1
Missing[a]	0	0	1	0
Animals surviving to study termination	41	38[e]	37[e]	36
Percent probability of survival at end of study	82	75	76	74
Mean survival (days)	666	651	650	657
Survival analysis	P=0.507	P=0.439	P=0.514	P=0.433

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

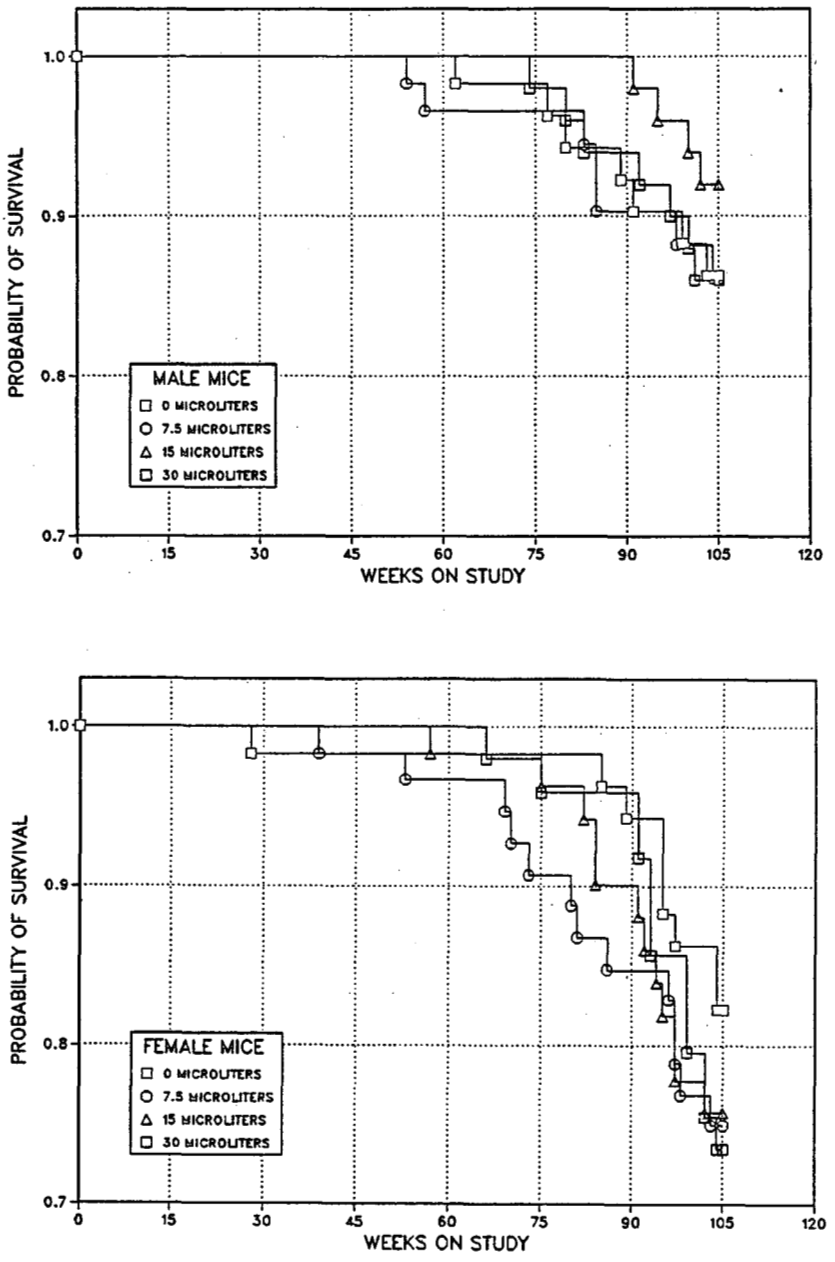


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Diethylphthalate Dermally for 2 Years

TABLE 10
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Diethylphthalate

Weeks on Study	0 μL		7.5 μL			15 μL			30 μL		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.7	60	21.2	98	60	21.2	98	60	21.1	97	60
2	22.7	60	22.3	98	60	22.3	98	60	22.2	98	60
3	23.6	60	23.4	99	60	23.3	99	60	23.3	99	60
4	23.8	60	23.7	100	60	23.4	98	60	23.5	99	60
5	24.6	60	24.4	99	59	24.1	98	60	24.2	98	60
6	25.3	60	24.8	98	59	24.9	98	60	25.1	99	60
7	26.0	60	25.4	98	59	25.4	98	60	25.6	99	60
8	26.6	60	26.3	99	59	26.2	99	60	26.3	99	60
9	27.1	60	26.7	99	59	26.5	98	60	26.4	97	60
10	27.6	60	27.3	99	59	27.0	98	60	27.0	98	60
11	28.2	60	27.8	99	59	27.6	98	60	27.5	98	60
12	28.7	60	28.2	98	59	28.0	98	60	28.1	98	60
13	29.3	60	28.8	98	59	28.6	98	60	28.5	97	60
17	30.7	60	30.4	99	59	30.3	99	60	29.8	97	60
21	32.1	60	31.6	98	59	31.6	98	60	31.1	97	60
25	33.7	60	33.1	98	58	33.1	98	60	32.6	97	60
29	34.4	60	33.9	99	58	33.6	98	60	33.5	97	60
33	34.4	60	33.8	98	58	33.6	98	60	33.3	97	60
37	35.9	60	35.4	99	58	35.0	98	60	34.7	97	60
41	36.7	60	36.3	99	58	36.1	98	60	35.9	98	60
45	37.2	60	36.7	99	58	36.6	98	60	36.1	97	60
49	37.4	60	36.8	98	58	36.5	98	60	36.3	97	60
53	38.0	60	37.1	98	58	37.1	98	60	37.1	98	60
57	38.2	60	37.4	98	57	37.3	98	60	37.1	97	60
61	39.5	60	38.7	98	56	38.5	98	60	38.3	97	60
65[a]	39.3	59	38.2	97	56	38.3	98	60	38.2	97	60
69	39.2	49	38.7	99	46	37.9	97	50	38.3	98	50
73	39.4	49	38.7	98	46	38.2	97	50	38.1	97	50
77	39.5	49	39.4	100	46	38.8	98	50	38.6	98	49
81	39.2	47	38.6	99	46	38.2	97	50	37.9	97	48
85	38.5	47	37.9	98	45	37.4	97	50	37.3	97	47
89	38.2	47	38.1	100	43	37.4	98	50	37.4	98	47
93	37.6	45	37.0	98	43	36.3	97	49	36.6	97	46
97	37.6	45	37.2	99	43	36.1	96	48	36.5	97	46
101	37.2	44	36.8	99	42	35.7	96	47	36.2	97	44
105	37.6	43	37.0	98	41	35.8	95	46	36.4	97	43
Mean for weeks											
1-13	25.8		25.4	98		25.3	98		25.3	98	
14-52	34.7		34.2	99		34.0	98		33.7	97	
53-105	38.5		37.9	98		37.4	97		37.4	97	

[a] Interim evaluation occurred during week 65.

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

Weeks on Study	0 μL		7.5 μL			15 μL			30 μL		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.1	60	17.0	99	60	17.2	101	60	17.1	100	60
2	18.4	60	18.4	100	60	18.6	101	60	18.2	99	60
3	19.6	60	19.4	99	60	19.9	102	60	19.6	100	60
4	20.1	60	19.6	98	60	20.2	101	60	20.2	101	60
5	20.7	60	20.6	100	60	21.2	102	60	21.0	101	60
6	21.4	60	21.4	100	60	21.7	101	60	22.0	103	60
7	21.9	60	21.7	99	60	22.2	101	60	22.3	102	60
8	22.3	60	22.3	100	60	22.9	103	60	22.6	101	60
9	23.2	60	22.9	99	60	23.3	100	60	22.9	99	60
10	23.5	60	23.1	98	60	23.7	101	60	23.3	99	60
11	24.0	60	23.4	98	60	24.1	100	60	24.0	100	60
12	24.2	60	23.8	98	60	24.5	101	60	24.4	101	60
13	24.8	60	24.5	99	60	25.1	101	60	24.9	100	60
17	26.2	60	26.0	99	60	26.4	101	60	26.2	100	60
21	28.0	60	27.4	98	60	28.1	100	60	27.6	99	60
25	29.6	60	29.2	99	60	29.7	100	60	29.2	99	60
29	30.2	59	30.2	100	60	30.6	101	59	30.4	101	60
33	30.9	59	30.4	98	60	30.7	99	59	30.5	99	60
37	32.2	59	31.7	98	60	32.3	100	59	31.8	99	59
41	33.4	59	33.0	99	59	33.3	100	59	32.7	98	59
45	33.8	59	33.3	99	59	33.8	100	59	33.5	99	59
49	34.1	59	33.7	99	59	34.3	101	59	33.9	99	59
53	34.9	59	34.6	99	59	35.2	101	59	34.7	99	59
57	35.4	59	34.9	99	58	35.3	100	59	34.8	98	59
61	36.6	59	36.1	99	58	36.8	101	58	36.1	99	59
65[a]	36.3	59	35.9	99	58	36.1	99	58	36.1	99	59
69	36.9	49	36.2	98	49	37.0	100	48	36.4	99	48
73	37.0	49	37.0	100	47	37.2	101	48	37.1	100	48
77	37.9	49	37.9	100	46	38.4	101	47	37.9	100	47
81	37.5	49	37.8	101	45	38.0	101	47	37.7	101	47
85	37.1	49	37.7	102	44	37.5	101	44	37.5	101	47
89	36.9	48	37.4	101	43	37.0	100	44	37.4	101	47
93	36.4	47	36.4	100	43	36.4	100	42	36.5	100	44
97	36.0	44	36.3	101	42	35.9	100	40	36.6	102	42
101	35.8	43	35.9	100	39	36.1	101	38	36.7	103	39
105	36.1	41	36.0	100	38	36.2	100	37	36.9	102	36
Mean for weeks											
1-13	21.6		21.4	99		21.9	101		21.7	100	
14-52	30.9		30.5	99		31.0	100		30.6	99	
53-105	36.5		36.4	100		36.7	101		36.6	100	

[a] Interim evaluation occurred during week 65.

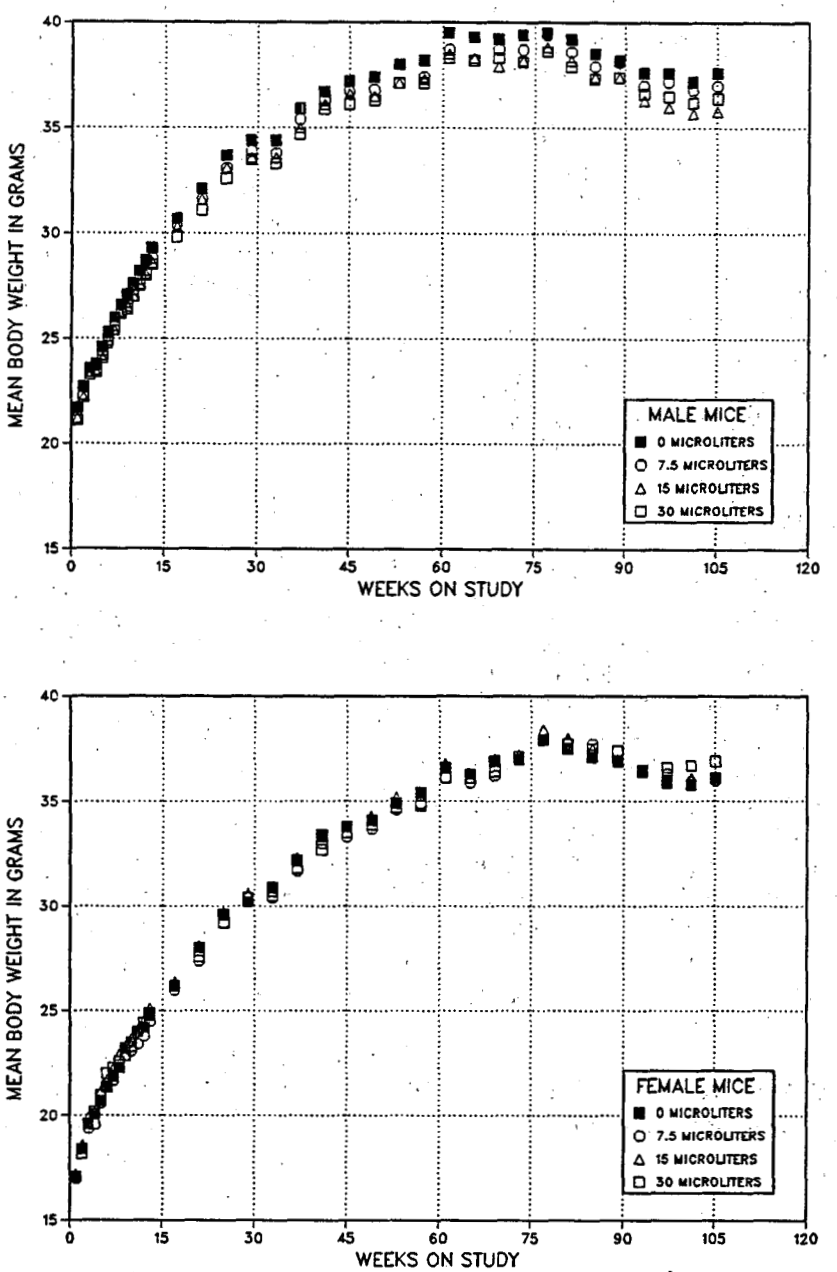


FIGURE 4
Growth Curves for Male and Female Mice Administered Diethylphthalate Dermally for 2 Years

Pathology Findings

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

Skin, Site of Application: No skin neoplasms were observed in dosed male mice. In female mice receiving 30 μL, one squamous cell carcinoma and one basal cell carcinoma were seen at the site of application (Table D1). The significance of these two neoplasms of differing biology is questionable. No morphological evidence of dermal toxicity was observed in male or female mice.

Liver: The incidences of hepatocellular adenomas in 7.5 and 15 μL females were greater than that in controls, but no significant dose-related trend was observed for either sex (Tables 12, C3, and D3). No significant increase in the incidence of hepatocellular carcinomas was observed in either male or female mice. The combined incidence of hepatocellular adenomas or carcinomas in 30 μL male mice was higher than that of controls (Tables 12 and C3). A positive dose-related trend of hepatocellular adenomas or carcinomas combined was also observed in male mice. The combined incidence of hepatocellular adenomas or carcinomas in 7.5 and 15 μL female mice was higher than that of controls with no dose-related trend (Tables 12 and D3).

Because the NTP's B6C3F$_1$ mouse historical database contains only two dermal studies using acetone as the vehicle control, historical data from control mice in feed studies were also used for comparison. These data suggest that the seemingly higher incidences of liver neoplasms observed in male mice in this study may reflect an unusually low control incidence of hepatocellular adenomas (male mice historical feed controls, adenoma: 24%, range 4%-60%; adenoma or carcinoma (combined): 36%, range 10%-68%; Table C4). Female mouse historical data are similar to the control females in this study (female mice feed control, adenomas: 12%, range 0%-33%; adenoma or carcinoma (combined): 17%, range 3%-42%; Table D4). Because the incidence of hepatocellular neoplasms in the 30 μL male mice was similar to the historical control mean, and because there was no dose response for liver neoplasms in female mice, these marginal increases were considered to be uncertain findings, providing only equivocal evidence of carcinogenic activity.

Some nonneoplastic proliferative lesions were identified. In particular, an increased incidence of basophilic foci was noted in 15 μL male mice (Table 12). The incidence of basophilic foci in female mice was not significantly greater than in controls (Table 12). As in the case of liver neoplasms, no dose-related trends were apparent. No increased incidence of neoplasms or nonneoplastic lesions was noted in male or female mice at the 15-month interim evaluation.

Female mice, but not male mice, had antibodies to Reovirus-3 at 18 months. Further, neither males nor females were positive for Reovirus-3 at 24 months, indicating that this was not a widespread infection in the colony. Experimental infections of young mice with Reovirus-3 may cause various lesions including hepatitis. However, there are no known pathologic changes associated with natural infections of Reovirus-3 (NRC, 1991).

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Dermal Study of Diethylphthalate

Dose (μL)	0	7.5	15	30
Male				
15-Month Interim Evaluation				
Liver[a]	10	3	1	10
Hepatocellular Adenoma[b]	1	2	1	2
Hepatocellular Carcinoma	0	0	0	1
2-Year Study				
Liver	50	50	50	50
Basophilic Focus	0	1	9**	3
Eosinophilic Focus	1	0	0	2
Clear Cell Focus	2	3	2	3
Mixed Cell Focus	0	0	1	0
Hepatocellular Adenoma				
Overall rate[c]	6/50 (12%)	11/50 (22%)	9/50 (18%)	12/50 (24%)
Adjusted rate[d]	14.0%	26.0%	19.6%	27.9%
Terminal rate[e]	6/43 (14%)	10/41 (24%)	9/46 (20%)	12/43 (28%)
First incidence (days)	730 (T)	576	730 (T)	730 (T)
Logistic regression test[f]	P=0.140	P=0.118	P=0.337	P=0.094
Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted rate	9.0%	8.9%	12.8%	14.6%
Terminal rate	3/43 (7%)	1/41 (2%)	5/46 (11%)	3/43 (7%)
First incidence (days)	635	576	714	556
Logistic regression test	P=0.170	P=0.623N	P=0.369	P=0.257
Hepatocellular Adenoma or Carcinoma[g]				
Overall rate	9/50 (18%)	14/50 (28%)	14/50 (28%)	18/50 (36%)
Adjusted rate	20.4%	31.7%	29.8%	38.1%
Terminal rate	8/43 (19%)	11/41 (27%)	13/46 (28%)	14/43 (33%)
First incidence (days)	635	576	714	556
Logistic regression test	P=0.040	P=0.144	P=0.206	P=0.034

(continued)

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

Dose (μL)	0	7.5	15	30
Female				
15-Month Interim Evaluation				
Liver	10	4	3	10
Hepatocellular Adenoma	3	0	0	1
Hepatocellular Carcinoma	0	0	0	1
2-Year Study				
Liver	50	51	50	50
Basophilic Focus	2	3	6	2
Clear Cell Focus	1	1	3	1
Eosinophilic Focus	1	4	3	3
Mixed Cell Focus	1	1	1	1
Hepatocellular Adenoma				
Overall rate	4/50 (8%)	12/51 (24%)	14/50 (28%)	10/50 (20%)
Adjusted rate	9.8%	30.6%	35.5%	24.8%
Terminal rate	4/41 (10%)	11/38 (29%)	12/37 (32%)	7/36 (19%)
First incidence (days)	730 (T)	675	586	456
Logistic regression test	P=0.127	P=0.017	P=0.006	P=0.075
Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	5/51 (10%)	6/50 (12%)	3/50 (6%)
Adjusted rate	8.8%	11.7%	14.4%	7.1%
Terminal rate	2/41 (5%)	2/38 (5%)	2/37 (5%)	0/36 (0%)
First incidence (days)	591	560	644	645
Logistic regression test	P=0.297N	P=0.603	P=0.457	P=0.484N
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	7/50 (14%)	16/51 (31%)	19/50 (38%)	12/50 (24%)
Adjusted rate	15.8%	37.8%	45.0%	28.6%
Terminal rate	5/41 (12%)	12/38 (32%)	14/37 (38%)	7/36 (19%)
First incidence (days)	591	560	586	456
Logistic regression test	P=0.231	P=0.029	P=0.005	P=0.161

°° Significantly different (P≤0.01) from the control group by logistic regression
(T) Terminal sacrifice
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Observed incidence of animals surviving until the end of the study
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for incurrent mortality
[f] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and the dosed group. The logistic regression analysis regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[g] Historical incidence for 2-year study with untreated control groups (mean ± standard deviation): (Feed) 531/1,466 (36.2% ± 14.1%); range 10%-68%; (Dermal, Acetone) 32/100 (32.0% ± 19.8%); range 18%-46%
[h] Historical incidence: (Feed) 247/1,462 (16.9% ± 10.7%); range 3%-42%; (Dermal, Acetone) 17/100 (17.0% ± 4.2%); range 14%-20%

1-YEAR INITIATION/PROMOTION STUDY OF DIETHYLPHTHALATE AND DIMETHYLPHTHALATE IN SWISS (CD-1®) MICE

Survival

A high incidence of mice in all TPA treated groups developed severe skin lesions which progressed to ulceration between days 25 and 60 of exposure. The TPA exposure concentrations and dosing regimen were adjusted to 0.025 mg/mL, two times per week at week 10. For TPA treated mice where ulcerative skin lesions persisted, an early, aggressive moribund sacrifice was conducted during weeks 20 and 21.

Estimates of the survival probabilities for male Swiss (CD-1®) mice are shown in Table 13 and the Kaplan-Meier curves in Figures 5a and 5b. Survival was significantly decreased in those mice treated with TPA and varied from 29% to 51% lower than that of the vehicle controls (acetone/acetone). Survival in other groups was similar to vehicle controls.

Body Weights and Clinical Findings

Concomitant body weight depressions occurred in most groups treated with TPA (Table 13, and Figures 6a and 6b). The most severe depression occurred in the initiation/promotion controls (DMBA/TPA). Mean body weights of mice treated only with either DEP or DMP (initiation controls or promotion controls) were similar to that of the vehicle controls (Table 13, and Figures 6a and 6b).

Skin at the site of application was examined for macroscopic changes before the beginning of the promotion regime and at weekly intervals thereafter. Macroscopic lesions generally appeared earlier and were more severe in groups treated with TPA. In these groups, skin irritation was evident at the site of application by 25 days of exposure, which subsequently developed into a severe life-threatening chronic exudative ulcerative dermatitis. These lesions persisted despite suspension of treatment. Irritation and ulceration at the site of application were also evident in promotion control mice treated with DEP or DMP. However, in general, the incidence was lower and length of the latency period increased.

Mice in groups receiving TPA also developed papillomatous nodular lesions within the site of application and in the adjacent skin. This was most prevalent in the positive controls (DMBA/TPA), but was also observed in other groups.

TABLE 13
Survival and Mean Body Weights of Male Mice in the 1-Year Initiation/Promotion Dermal Study of Diethylphthalate/Dimethylphthalate[a]

Group	Survival[b]	Mean Body Weight (g)			Final Weight Relative to Vehicle Control (%)
		Initial	Final	Change	
DMP Initiation					
Acetone/Acetone	35/50	32.0	49.4	17.4	
DMBA/Acetone	38/50	32.2	48.8	16.6	99
DMP/Acetone	38/50	32.2	47.9	15.7	97
DMP/TPA	13/50	32.5	46.7	14.2	95
DMP Promotion					
Acetone/Acetone	35/50	32.0	49.4	17.4	
Acetone/TPA	18/50	32.1	48.3	16.2	98
Acetone/DMP	40/50	32.6	47.3	14.7	96
DMBA/DMP	36/50	32.2	48.7	16.5	99
DEP Initiation					
Acetone/Acetone	35/50	32.0	49.4	17.4	
DMBA/Acetone	38/50	32.2	48.8	16.6	99
DEP/Acetone	35/50	32.4	48.4	16.0	98
DEP/TPA	14/50	32.3	46.1	13.8	93
DEP Promotion					
Acetone/Acetone	35/50	32.0	49.4	17.4	
Acetone/TPA	18/50	32.1	46.2	14.1	94
Acetone/DEP	38/50	32.2	51.6	19.4	104
DMBA/DEP	42/50	32.6	47.6	15.0	96
Initiation/Promotion Control					
Acetone/Acetone	35/50	32.0	49.4	17.4	
DMBA/TPA	10/50	32.0	41.6	9.6	84

[a] TPA = 12-*O*-tetradecanoylphorbol-13-acetate DMBA = 7,12-dimethylbenz(a)anthracene DMP = dimethylphthalate DEP = diethylphthalate
[b] Number of animals surviving at 1 year/number initially in group

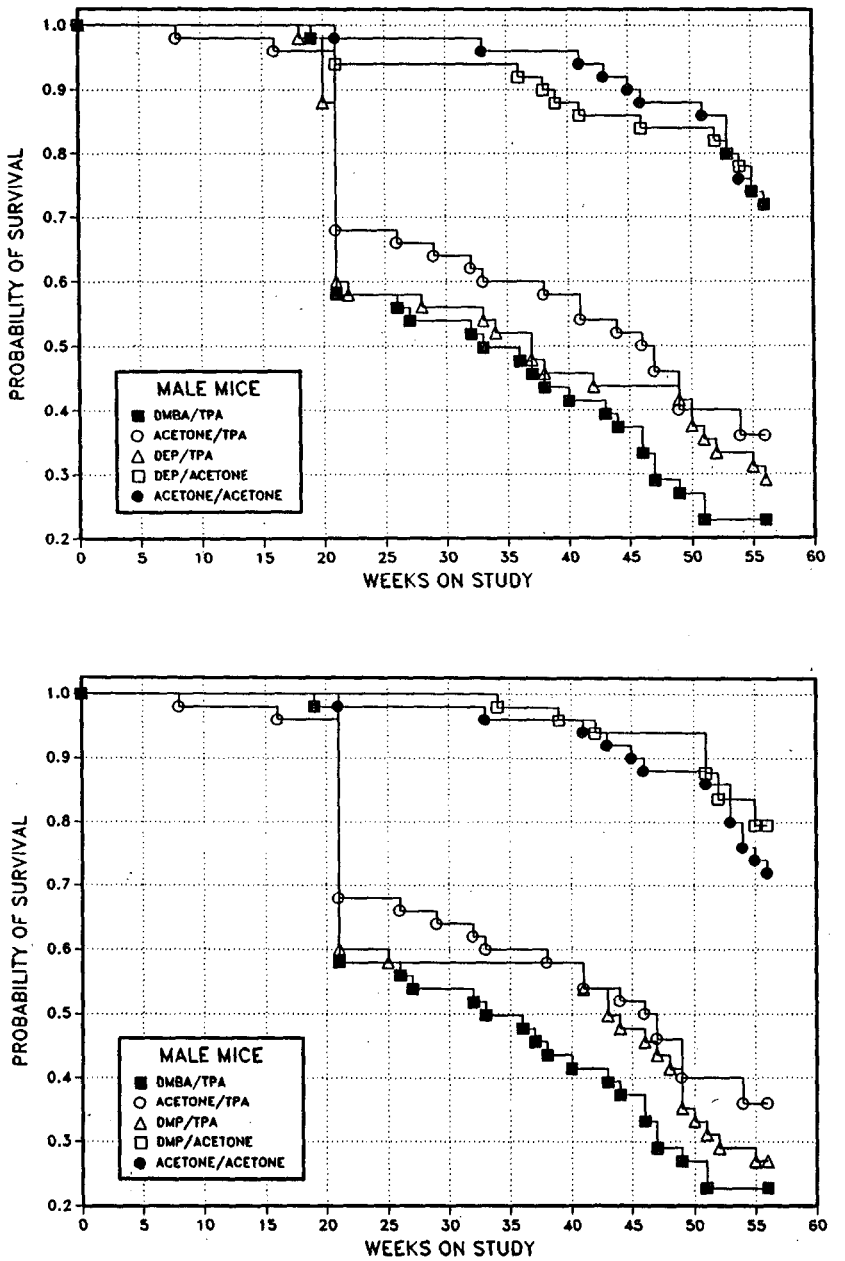


FIGURE 5a
Kaplan-Meier Survival Curves for Male Mice in the 1-Year Initiation/Promotion Study

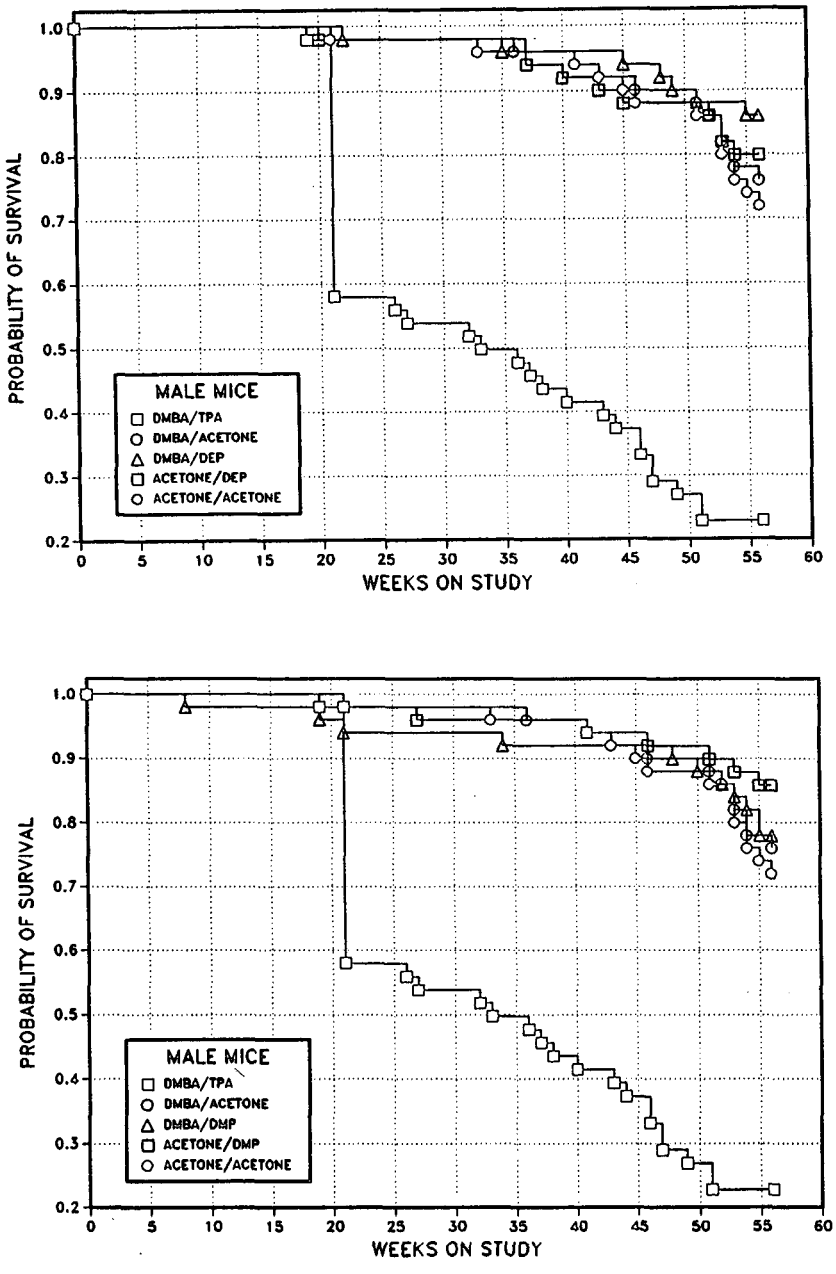


FIGURE 5b
Kaplan-Meier Survival Curves for Male Mice in the 1-Year Initiation/Promotion Study

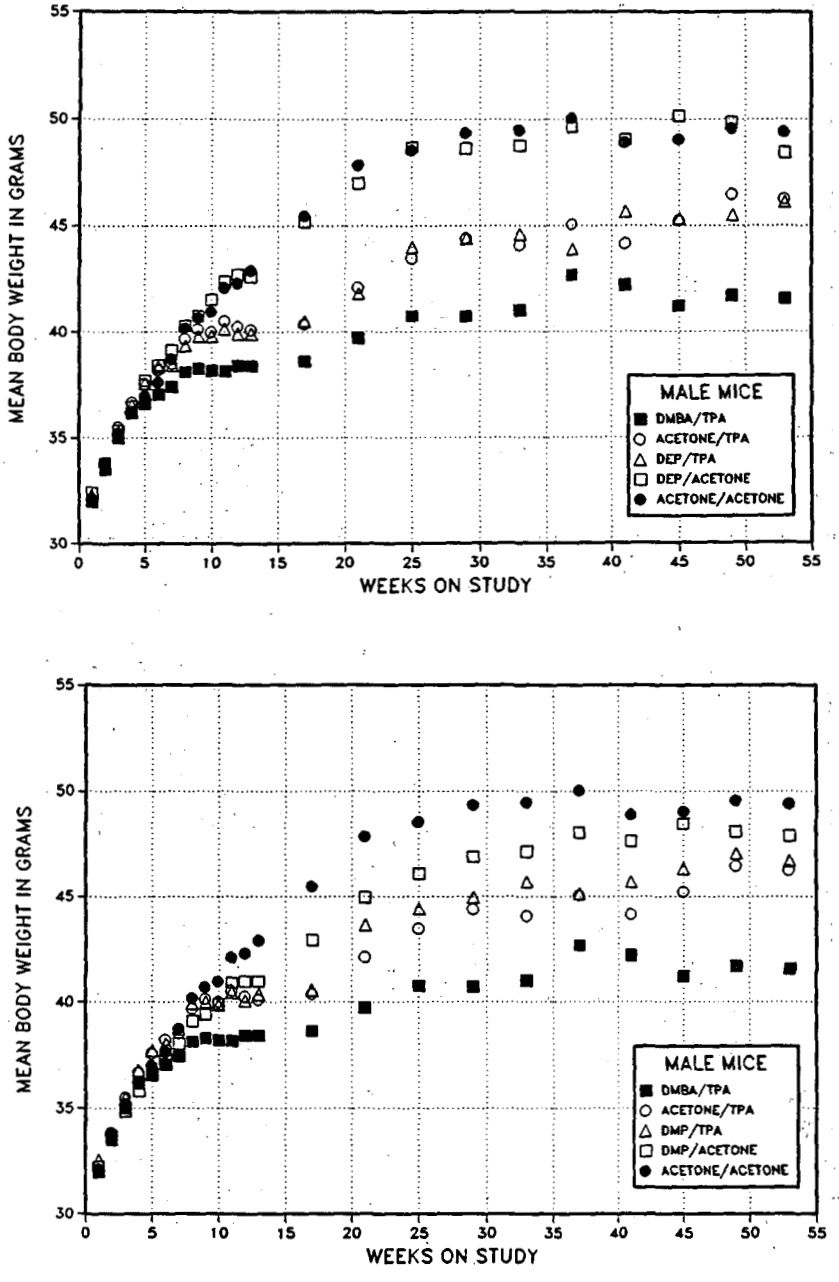


FIGURE 6a
Growth Curves for Male Mice in the 1-Year Initiation/Promotion Study

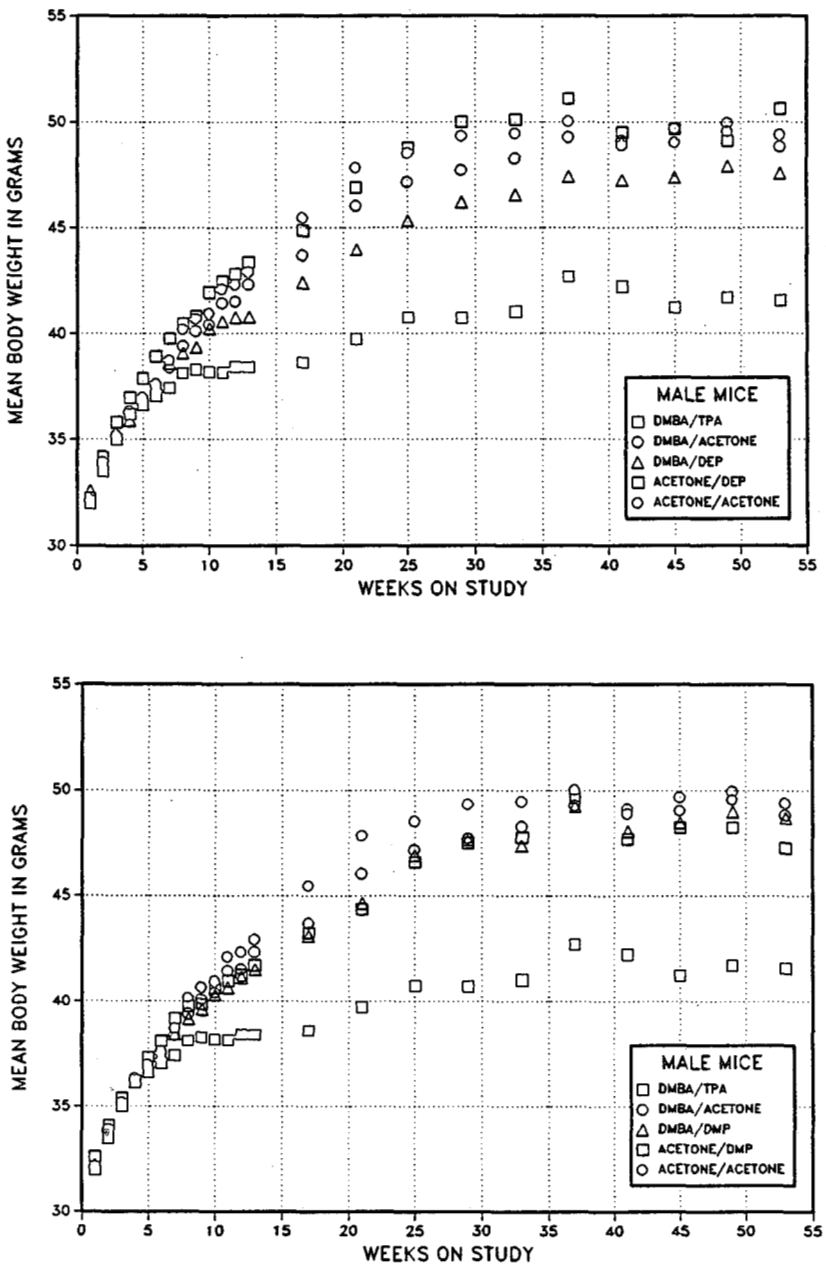


FIGURE 6b
Growth Curves for Male Mice in the 1-Year Initiation/Promotion Study

Pathology Findings

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin and urinary bladder. Skin at the site of application and adjacent to the site of application was examined microscopically. All skin masses were counted and a maximum of five masses per animal were selected and identified for histopathologic examination. Lesions described below and considered to be related to chemical treatment include cutaneous neoplasms (squamous cell papillomas, squamous cell carcinomas, keratoacanthomas, and sebaceous gland adenomas) and ulcerative dermatitis (acanthosis, hyperkeratosis, ulceration, subacute inflammation, and exudation).

Skin, Site of Application: Acanthosis was the predominant and most consistently occurring lesion and varied from focally marked epidermal thickening and folding to irregular epidermal thickening involving the entire surface of the section. These lesions were present in all groups but were considerably more prevalent in those groups promoted with TPA (Table 14). Almost invariably, acanthosis was accompanied by variable hyperkeratosis. While some acanthomatous lesions lacked ulceration, ulceration was also a common finding (Table 14). Often these acanthomatous, ulcerative lesions extended beyond the site of application. Ulceration within the site of application was accompanied by intense, subacute inflammation that extended deeply into the dermis. Superficially, the ulcers were covered by a coagulum composed of serofibrinous exudate, erythrocytes, dead leukocytes and necrotic cellular debris. Polymorphonuclear leukocytes predominated toward the surface (superficial dermis) of the ulcers, while mononuclear leukocytes predominated in the deeper more fibrotic portions. Occasional abscesses developed within the dermis or within the subcutis.

TABLE 14
Incidences of Skin Lesions of Male Mice in the 1-Year Initiation/Promotion Dermal Study of Diethylphthalate/Dimethylphthalate[a]

	Acanthosis	Ulceration	Exudate	Hyperkeratosis
Vehicle Control				
Acetone/Acetone	8/50	2/50	4/50	1/50
Initiation Controls				
Acetone/DEP	9/50	5/50	8/50	6/50
Acetone/DMP	11/49	6/49	7/49	4/49
Promotion Controls				
DEP/Acetone	14/49	6/49	11/49	8/49*
DMP/Acetone	9/50	3/50	5/50	1/50
DEP or DMP Initiation				
Acetone/TPA	47/50*	23/50*	25/50*	34/50*
DEP/TPA	43/49*	25/49*	32/49*	31/49*
DMP/TPA	47/49*	27/49*	30/49*	34/49*
DEP or DMP Promotion				
DMBA/Acetone	18/50*	7/50	10/50	13/50*
DMBA/DEP	6/50	5/50	5/50	5/50
DMBA/DMP	7/50	3/50	2/50	2/50
Initiation/Promotion Control				
DMBA/TPA	46/49*	22/49*	32/49*	40/49*

* Significantly different ($P \leq 0.05$) from the vehicle control group (acetone/acetone) by logistic regression
[a] Incidences are for lesions which occurred at the site of application

In addition to the site of application, similar nonneoplastic lesions were observed in the skin adjacent to the site of application. The pattern of occurrence was similar to that at the site of application, the incidence of lesions being considerably greater for the TPA treated groups and less among the other treatment groups (Table 14). The incidence of nonneoplastic lesions in the control skin was negligible.

Cutaneous neoplasms that developed at the site of application were primarily squamous cell papillomas and squamous cell carcinomas. Squamous cell papillomas, often multiple, were the most prevalent of the skin neoplasms. Typical squamous cell papillomas were exophytic, arborizing, polypoid proliferations of the acanthotic, hyperkeratotic epidermis supported by a core of fibrovascular tissue that was contiguous with the subjacent dermis. The squamous epithelial cells were orderly in arrangement; however, the thickness of the epithelium varied. In most instances, the squamous cell papillomas were pedunculated arising from a single stalk, but occasionally were more broad based or sessile.

The highest incidence of both squamous cell papillomas and squamous cell carcinomas occurred among the initiation/promotion control animals initiated with DMBA and promoted with TPA. Rarely were squamous cell carcinomas observed in any other group (Table 15). Squamous cell carcinomas were generally well differentiated, consisting of proliferating nests or anastomosing cords of neoplastic squamous epithelium, which projected into the dermis. Often, nests of neoplastic cells had central concentrically arranged (keratin pearl) keratinization. Individual cell keratinization was also demonstrable. Cellular and nuclear atypia were often present and the cells in some areas of the neoplasms were spindle shaped.

Among the five control groups (vehicle control, DEP initiation control, DMP initiation control, DEP promotion control, or DMP promotion control), only one skin squamous cell papilloma and one squamous cell carcinoma were observed (Table 15). TPA, used in this study due to its demonstrated activity as a skin tumor promoter, induced a minor increase in the incidence of squamous cell papillomas.

DMBA, used in this study as an initiator, also demonstrated some evidence of complete carcinogenicity, inducing nonsignificant increased incidences of both benign and malignant skin neoplasms (Table 15). The incidence of squamous cell papillomas, squamous cell carcinomas, and of squamous cell papillomas and carcinomas combined were significantly greater in the initiation/promotion control group than in either the DMBA initiation control group or the TPA promotion control group.

In contrast to the initiation/promotion control, no evidence of either initiating or promoting activity was observed for either DEP or DMP in this study. Only rarely were squamous cell carcinomas observed in the DEP or DMP initiation groups (Table 15). Of the groups initiated with either DEP or DMP, only those promoted with TPA developed increased incidences of squamous cell papillomas. Likewise, among the groups initiated with DMBA and promoted with either DEP or DMP, the incidence of squamous cell papillomas was low. No squamous cell carcinomas were detected in these groups, despite their rare occurrence in initiation controls.

Other: In DMP treated mice, the incidences of neoplasms in the DMP initiation control group and the DMP promotion control group were similar to those of the vehicle control. At skin sites other than the site of application, significantly fewer incidences of dermal acanthosis, exudation, and ulceration were observed in the DMP promotion control than in the vehicle control (Table 14). Microscopic calculi were more frequently detected in the urinary bladder of DMP promotion control mice (6/46) than in that of the vehicle controls (0/47). No other dose-related lesions were observed in DMP initiation control or DMP initiation control groups.

Based on the incidence of skin neoplasms diagnosed histologically and the multiplicity of skin neoplasms, there was no suggestion that either DEP or DMP was able to initiate skin carcinogenesis when chronically promoted by TPA. Sensitivity for detection of initiation effects may have been decreased by the lower survival among TPA treated mice. Further, there was no evidence that either DEP or DMP was able to promote skin carcinogenesis in skin previously initiated with DMBA.

TABLE 15
Incidences of Skin Neoplasms of Male Mice in the 1-Year Initiation/Promotion Dermal Study of Diethylphthalate/Dimethylphthalate[a]

	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Vehicle Control			
Acetone/Acetone	0/50	0/50	0/50
Initiation Controls			
Acetone/DEP	0/50	0/50	0/50
Acetone/DMP	0/49	0/49	0/49
Promotion Controls			
DEP/Acetone	1/50	0/50	1/50
DMP/Acetone	0/50	0/50	0/50
DEP or DMP Initiation			
Acetone/TPA	5/50*	0/50	5/50*
DEP/TPA	3/49*	0/49	3/49*
DMP/TPA	3/49*	1/49	4/49*
DEP or DMP Promotion			
DMBA/Acetone	1/50	2/50	3/50
DMBA/DEP	2/50	0/50	2/50
DMBA/DMP	1/50	0/50	1/50
Initiation/Promotion Control			
DMBA/TPA	23/49*▲□	7/49*▲□	25/49*▲□

* Significantly different (P≤0.05) from the vehicle control group (acetone/acetone) by logistic regression
▲ Significantly different (P≤0.05) from the promotion control group (DMBA/acetone) by logistic regression
□ Significantly different (P≤0.05) from the initiation control group (acetone/TPA) by logistic regression
[a] Incidences are for lesions which occurred at the site of application

GENETIC TOXICOLOGY

Diethylphthalate (10 to 10,000 μg/plate) was tested by two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (Table E4; Zeiger *et al.*, 1985). Testing was performed using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. High dose was limited by toxicity to 3,333 μg/plate in the first laboratory, but reached the maximum concentration (10,000 μg/plate) permitted by the testing protocol in the second laboratory. Negative results were obtained with diethylphthalate at both laboratories in all four tester strains.

In cytogenetic tests with cultured Chinese hamster ovary cells, diethylphthalate induced sister chromatid exchanges in the presence of Aroclor 1254-induced rat liver S9 (Table E5) but not chromosomal aberrations, with or without S9 (Table E6). Significant increases in sister chromatid exchanges were obtained at concentrations of 167 to 750 μg/mL diethylphthalate. Cell cycle delay, indicative of chemical-related toxicity, was observed only at the 750 μg/mL level. The small dose-related increase in chromosomal aberrations observed in the one trial without S9 was insufficient for a positive call because no single dose was significantly elevated above the control, and the trend test P value was not less than 0.003.

Dimethylphthalate (33 to 6,666 μg/plate) did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Zeiger *et al.*, 1985).

In cytogenetic tests with cultured Chinese hamster ovary cells, dimethylphthalate induced sister chromatid exchanges in the presence, but not the absence, of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E2; Loveday *et al.*, 1990). Except for the positive response noted at 151 μg/mL in the first trial with S9, concentrations above 1,000 μg/mL were necessary to induce an increase in sister chromatid exchanges. The increases in sister chromatid exchanges observed after treatment with dimethylphthalate, although small, were well correlated with dose. Dimethylphthalate was less toxic to Chinese hamster ovary cells than was diethylphthalate in these studies.

No induction of chromosomal aberrations was observed in Chinese hamster ovary cells treated with dimethylphthalate with or without S9 (Table E3; Loveday *et al.*, 1990). Two trials were conducted with S9, one using the standard 12-hour incubation period and the second using an extended incubation time of 20.5 hours to ensure that harvested Chinese hamster ovary cells were exposed to dimethylphthalate for at least one complete cell cycle. No significant increase in chromosomal aberrations was noted in either trial, where the highest dose tested was 5,100 μg/mL.

In conclusion, neither dimethylphthalate nor diethylphthalate induced mutations in *Salmonella* or chromosomal aberrations in Chinese hamster ovary cells. However, both chemicals induced sister chromatid exchanges in Chinese hamster ovary cells in the presence of S9. A comparative evaluation of *in vitro* genetic toxicity and rodent bioassay test results by the NTP showed that, although the positive sister chromatid exchange test might indicate a potential for *in vivo* DNA damage, this endpoint is highly sensitive and does not correlate well with carcinogenic effects in rodents (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). Only 64% of chemicals which induced sister chromatid exchanges *in vitro* were also carcinogenic in rats and/or mice. Thus, positive results in the sister chromatid exchange test have a low positive predictivity for carcinogenicity in rodents. The negative results obtained in the other *in vitro* genetic toxicity tests with dimethylphthalate and diethylphthalate do not further aid in classifying the chemicals as to their activity in the rodent bioassay. In the NTP evaluation of *in vitro* genetic toxicity tests, only about 50% of the nonmutagens were also found to be noncarcinogens.

DISCUSSION AND CONCLUSIONS

Diethylphthalate (DEP) and dimethylphthalate (DMP) are phthalate plasticizers used in the manufacture of a variety of products such as vinyl swimming pools, vinyl seats, safety glass, toothbrushes, toys, and clothing. DEP is also used in cosmetics such as eye shadows, perfumes and fragrances, hair sprays, and nail polishes. Additionally, DEP and DMP are primary ingredients or carriers in the manufacture of nonplasticized products such as solvents, varnishes, dyes, perfumes, coating agents for foodstuffs, and insecticides. Because of the high exposure potential and lack of long-term toxicity or carcinogenicity information, the U.S. Environmental Protection Agency nominated DEP to the NTP for testing.

This report presents no evidence for chronic toxicity or carcinogenicity at the site of application by DEP (104 weeks in rats and mice) or DMP (52 weeks in mice). These studies also included examination of both DEP and DMP for activity as initiators or promoters in a dermal initiation/promotion protocol. DEP and DMP were negative for skin carcinogenesis despite recent evidence suggesting that a related phthalate, diethylhexylphthalate, activates growth-regulatory signal transduction pathways in hepatic epithelial cells leading to the induction of the immediate-early nuclear proto-oncogenes *fos* and *jun*, potentially through a pathway involving protein kinase C (Ledwith *et al.*, 1993).

Systemically, however, the marginal increase in hepatocellular neoplasms induced by DEP in male and female mice merits further consideration. Previous studies have demonstrated the positive hepatocarcinogenicity of the related chemicals di(2-ethylhexyl)phthalate (DEHP; NTP, 1982a) and di(2-ethylhexyl)adipate (DEHA; NTP, 1982b). The route of chemical exposure (dermal) in the current DEP and DMP studies differed from the DEHP and DEHA feed studies. Doses of DEP and DMP administered to rats and mice in these studies were limited primarily by volume considerations and not systemic toxicity. The highest mouse dermal exposure was 30 μL per day (approximately 1.3 g/kg body weight per day). Estimates from dermal toxicokinetic studies suggest that approximately 20% of the applied dose may have been absorbed daily (Elsisi *et al.*, 1989). Previous DEHP feed studies (positive for hepatocarcinogenicity in male and female mice at 0.6%, and male and female rats at 1.2%; NTP, 1982a) and in DEHA feed studies (positive in male and female mice at 2.5%; NTP, 1982b) used similar daily dietary dosages (e.g., DEHP mice: 1.3 to 1.8 g/kg body weight per day). Unlike dermal studies, rapid, extensive absorption of phthalates occurs through the oral route of exposure (International Labour Office, 1983). The site of application was not occluded, so a portion of the dose administered may have been ingested during grooming.

DEP is considered a weak peroxisome proliferator (Moody and Reddy, 1978, 1982). Many peroxisome proliferators have induced hepatocellular neoplasia in long-term rodent studies; however, the mechanism of action of this class of chemicals is still poorly understood (Conway *et al.*, 1989). Neither peroxisome proliferation nor enhanced hepatocellular replication were estimated in this study, two physiological responses associated previously with the hepatocarcinogenic activity of peroxisome proliferators in rodents. Hepatomegaly and hepatocellular hypertrophy were observed in the higher dose groups of rats and mice in the 4-week studies. These effects are often a component of other pleiotropic responses induced by peroxisome-proliferating chemicals such as proliferation of smooth endoplasmic reticulum, induction of microsomal enzymes, peroxisome proliferation, and enhanced cell replication. Liver weight increases were not observed at lower doses in the 4-week studies or in any dose group at the 15-month interim evaluation of the 2-year studies.

The induction of hepatic neoplasms in rats by peroxisome proliferators has been associated with the promotion of altered basophilic foci (Cattley *et al.*, 1991). An increased incidence of basophilic foci was observed in male mice in the 2-year study; however, no dose-related trend was apparent and no statistically significant increased incidence was observed in female mice. Altered hepatic foci incidence values are an insensitive measure of liver foci increases and

the preferred method, stereological evaluation, has been employed frequently in initiation/promotion models of hepatocarcinogenesis (Cattley and Popp, 1989). It is also unknown whether basophilic foci observed in mice possess an important biologic role in neoplasm progression, as has been suggested for the rat following peroxisome proliferator exposure (Marsman and Popp, 1994).

With no significant effect of DEP on survival or body weight of female rats, the decreased incidence of mammary gland fibroadenomas may be an effect attributable to chemical treatment. Hormonal alterations have been implicated in the reproductive toxicity of several other phthalates (testicular germinal atrophy, ovarian follicular cysts; Heindel and Powell, 1992) and in the testicular carcinogenicity of several other peroxisome proliferators (Fitzgerald *et al.*, 1981; Biegel *et al.*, 1992). However no reports of peroxisome proliferator-induced effects on mammary gland fibroadenomas were found in the literature. The potent peroxisome proliferator and adrenal steroid hormone, dehydroxyepiandrosterone (DHEA),is known to have anticarcinogenic properties in addition to its carcinogenic properties (Rao *et al.*, 1992).

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diethylphthalate in male or female F344/N rats receiving 100 or 300 μL. The sensitivity of the male rat study was reduced due to low survival in all groups. There was *equivocal evidence of carcinogenic activity* of diethylphthalate in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms, primarily adenomas.

In an initiation/promotion model of skin carcinogenesis, there was no evidence of initiating activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. Further, there was no evidence of promotion activity of diethylphthalate or dimethylphthalate in male Swiss (CD-1®) mice. The promoting activity of TPA following DMBA initiation was confirmed in these studies.

Minor dermal acanthosis was observed following dermal application of diethylphthalate in male and female F344/N rats dosed for 2 years and in male Swiss (CD-1®) mice dosed for 1 year.

* 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.

REFERENCES

Agarwal, D.K., Lawrence, W.H., Nunez, L.J., and Autian, J. (1985). Mutagenicity evaluation of phthalic acid esters and metabolites in *Salmonella typhimurium* cultures. *J. Toxicol. Environ. Health* 16, 61-69.

Agency for Toxic Substances and Disease Registry (ATSDR) (1993). Toxicological profile for diethyl phthalate, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, draft version.

American Conference of Governmental Industrial Hygienists (ACGIH) (1991). *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 1991-1992.* Cincinnati, OH.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

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

Autian, J. (1973). Toxicity and health threats of phthalate esters: Review of the literature. *Environ. Health Perspect.* 4, 3-26.

Autian, J. (1980). Plastics. In *Casarett and Doull's Toxicology: The Basic Science of Poisons*, (J. Doull, C.D. Klaassen, and M.O. Amdur, Eds.), 2nd ed., pp. 531-556. Macmillan Publishing Co., Inc., New York.

Biegel, L.B., Hurtt, M.E., Frame, S.R., Applegate, M., O'Connor, J.C., and Cook, J.C. (1992). Comparison of the effects of Wyeth-14,643 in Crl:CD BR and Fisher-344 rats. *Fundam. Appl. Toxicol.* 19, 590-597.

Blevins, R.D., and Taylor, D.E. (1982). Mutagenicity screening of twenty-five cosmetic ingredients with the Salmonella/microsome test. *J. Environ. Sci. Health.* A17, 217-239.

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

The British Industrial Biological Research Association (BIBRA) Working Group (1989). Diethyl phthalate: Toxicity profile.

Brown, D., Butterworth, K.R., Gaunt, I.F., Grasso, P., and Gangolli, S.D. (1978). Short-term oral toxicity study of diethyl phthalate in the rat. *Food Cosmet. Toxicol.* 16, 415-422.

Callahan, M.A., Slimak, M.A., and Gabel, N.W. (1979). Water-related environmental fate of 129 priority pollutants. EPA-440/4 79-029a. Vol. I, pp. 94-95. U.S. Environmental Protection Agency, Washington, DC.

Castle, L., Mercer, A.J., Startin, J.R., and Gilbert, J. (1988). Migration from plasticized films into foods: 3. Migration of phthalate, sebacate, citrate and phosphate esters from films used for retail food packaging. *Food Addit. Contam.* 5, 9-20.

Castle, L., Mayo, A., and Gilbert, J. (1989). Migration of plasticizers from printing inks into foods. *Food Addit. Contam.* 6, 437-443.

Castle, L., Gilbert, J., and Eklund, T. (1990). Migration of plasticizer from poly(vinyl chloride) milk tubing. *Food Addit. Contam.* 7, 591-596.

Cattley, R.C., and Popp, J.A. (1989). Differences between the promoting activities of the peroxisome proliferator Wy-14,643 and phenobarbital in rat liver. *Cancer Res.* 49, 3246-3251.

Cattley, R.C., Marsman, D.S., and Popp, J.A. (1991). Age-related susceptibility in the carcinogenic effect of the peroxisome proliferator Wy-14,643 in rat liver. *Carcinogenesis* 12, 469-473.

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

Conway, J.G., Cattley, R.C., Popp, J.A., and Butterworth, B.E. (1989). Possible mechanisms in hepatocarcinogenesis by the peroxisome proliferator di(2ethylhexyl)phthalate. *Drug Metab. Rev.* **21**, 65-102.

Cosmetic Ingredient Review Panel (CIRP) (1985). Final report on the safety assessment of dibutyl phthalate, dimethyl phthalate, and diethyl phthalate. *J. Am. Coll. Toxicol.* **4**, 267-303.

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

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

DeVault, D.S. (1985). Contaminants in fish from Great Lakes harbors and tributary mouths. *Arch. Environ. Contam. Toxicol.* **14**, 587-594.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **32**, 236-248.

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

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

Elsisi, A.E., Carter, D.E., and Sipes, I.G. (1989). Dermal absorption of phthalate diesters in rats. *Fundam. Appl. Toxicol.* **12**, 70-77.

Fitzgerald, J.E., Sanyer, J.L., Schardein, J.L., Lake, R.S., McGuire, E.J., and de la Iglesia, F.A. (1981). Carcinogen bioassay and mutagenicity studies with the hypolipidemic agent gemfibrozil. *JNCI* **67**, 1105-1116.

Florin, I., Rutberg, L., Curvall, M., and Enzell, C.R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology* **15**, 219-232.

Food Research Laboratories, Inc. (1955). Toxicological studies of diethyl phthalate. Laboratory No. 67567. Celanese Corp. of America. Summit Research Laboratories, Summit, NJ.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

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

Gleiberman, S.E., Kotova, I.A., Nikolaev, G.M., and Iurchenko, V.V. (1978). Pharmacokinetics of dimethylphthalate [in Russian]. *Med. Parazitol. Parazit. Bolezni.* **47**, 58-63.

Gollamudi R., Lawrence, W.H., Rao, R.H., and Autian, J. (1985). Effects of phthalic acid esters on drug metabolizing enzymes of rat liver. *J. Appl. Toxicol.* **5**, 368-371.

Hansch, C. and Leo, A.J., Eds. (1985). *Constants for Substituent Correlation Analysis in Chemistry and Biology.*, John Wiley and Sons, New York

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

Hathway, D.E. (1972). Biotransformations. Part 12: Other Compounds. In *Foreign Compound Metabolism in Mammals. Volume 2: A Review of the Literature Published in 1970 and 1971*, p. 315. The Chemical Society, London.

Hawley, G.G., Ed. (1981). *The Condensed Chemical Dictionary*, 10th ed. Van Nostrand Reinhold Company, New York.

Heindel, J.J., and Powell, C.J. (1992). Phthalate ester effects on rat Sertoli cell function *in vitro*: Effects of phthalate side chain and age of animal. *Toxicol. Appl. Pharmacol.* 115, 116-123.

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

Howard, P.H., Banerjee, S., and Robillard, K.H. (1985). Measurement of water solubilities, octanol/water partition coefficients and vapor pressures of commercial phthalate esters. *Env. Tox. Chem.* 4, 653-661.

International Labour Office (1983). *Encyclopedia of Occupational Health and Safety*, Vol. I and II. International Labour Office, Geneva, Switzerland.

Ioku, T., *et al.* (1976). [In Japanese]. *Yakuri To Chiryo* 4, 510-514.

Ishidate, M., Jr., and Odashima, S. (1977). Chromosome tests with 134 compounds on Chinese hamster cells in vitro: A screening test for chemical carcinogens. *Mutat. Res.* 48, 337-354.

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

Kamrin, M.A., and Mayor, G.H. (1991). Diethyl phthalate: A perspective. *J. Clin. Pharmacol.* 31, 484-489.

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

Kayser, R.D., Sterling, D., and Viviani, D., Eds. (1982). *Intermediate Priority Pollutant Guidance Documents.* U.S. Environmental Protection Agency, Washington, DC.

Kozumbo, W.J., and Rubin, R.J. (1991). Mutagenicity and metabolism of dimethyl phthalate and its binding to epidermal and hepatic macromolecules. *J. Toxicol. Environ. Health* 33, 29-46.

Kozumbo, W.J., Kroll, R., and Rubin, R.J. (1982). Assessment of the mutagenicity of phthalate esters. *Environ. Health Perspect.* 45, 103-109.

Lake, B.G., Phillips, J.C., Linnell, J.C.J., and Gangolli, S.D. (1977). The *in vitro* hydrolysis of some phthalate diesters by hepatic and intestinal preparations from various species. *Toxicol. Appl. Pharmacol.* 39, 239-248.

Lamb, J.C.,IV, Chapin, R.E., Teague, J., Lawton, A.D., and Reel, J.R. (1987). Reproductive effects of four phthalic acid esters in the mouse. *Toxicol. Appl. Pharmacol.* 88, 225-269.

Ledwith, B.J., Manam, S., Troilo, P., Joslyn, D.J., Galloway, S.M., and Nichols, W.W. (1993). Activation of immediate-early gene expression by peroxisome proliferators in vitro. *Mol. Carcinog.* 8, 20-27.

Lee H.-Y., Kalmus, G.W., and Levin, M.A. (1974). Effects of phthalate esters (plasticizers) on chick embryos and chick embryonic cells. *Growth* 38, 301-312.

Lefaux, R. (1968). *Practical Toxicology of Plastics* (P.P. Hopf, Ed.), pp. 136. CRC Press, Cleveland, OH.

Loveday, K.S., Anderson, B.E., Resnick, M.A., and Zeiger, E. (1990). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. *Environ. Mol. Mutagen.* 16, 272-303.

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

McFall, J.A., Antoine, S.R., and DeLeon, I.R. (1985). Base-neutral extractable organic pollutants in biota and sediments from Lake Ponchartrain. *Chemosphere* 14, 1561-1569.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* 79, 639-648.

Mackison, F.W., Stricoff, R.S., and Partridge, L.J., Jr., Eds. (1981). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS (NIOSH) Publication No. 81-123 (3 vols.). U.S. Government Printing Office, Washington, DC.

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

Marsman, D.S., and Popp, J.A. (1994). Biological potential of basophilic hepatocellular foci and hepatic adenoma induced by the peroxisome proliferator, Wy-14,643. *Carcinogenesis* **15**, 111-117.

Menzie, C.M. (1974). Metabolism of pesticides, an update. Special Scientific Report, Wildlife No. 184. U.S. Department of the Interior, Fish, Wildlife Service, Washington, DC.

The Merck Index (1983). 10th ed. (M. Windholz, Ed.), Merck and Company, Rahway, N.J.

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

Moody, D.E., and Reddy, J.K. (1978). Hepatic peroxisome (microbody) proliferation in rats fed plasticizers and related compounds. *Toxicol. Appl. Pharmacol.* **45**, 497-504.

Moody, D.E., and Reddy, J.K. (1982). Serum triglyceride and cholesterol contents in male rats receiving diets containing plasticizers and analogues of the ester 2-ethylhexanol. *Toxicol. Lett.* **10**, 379-383.

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

National Cancer Institute (NCI) (1979a). Bioassay of Dimethyl Terephthalate for Possible Carcinogenicity (CAS No. 120-61-6). Technical Report Series No. 121. NIH Publication No. 79-1376. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1979b). Bioassay of Phthalic Anhydride for Possible Carcinogenicity (CAS No. 85-44-9). Technical Report Series No. 159. NIH Publication No. 79-1715. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1979c). Bioassay of Phthalamide for Possible Carcinogenicity (CAS No. 88-96-0). Technical Report Series No. 161. NIH Publication No. 79-1717. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

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

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

National Research Council (NRC) (1991). *Companion Guide to Infections Diseases of Mice and Rats.* pp. 43.

National Toxicology Program (NTP) (1982a). Carcinogenesis Bioassay of Di(2-Ethylhexyl)Phthalate (CAS No. 117-81-7) in F344 Rats and B6C3F$_1$ Mice (Feed Study). Technical Report Series No. 217. NIH Publication No. 82-1773. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1982b). Carcinogenesis Bioassay of Di(2-Ethylhexyl)Adipate (CAS No. 103-23-1) in F344 Rats and B6C3F$_1$ Mice (Feed Study). Technical Report Series No. 212. NIH Publication No. 81-1768. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1982c). Carcinogenesis Bioassay of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344/N Rats and B6C3F$_1$ Mice (Feed Study). Technical Report Series No. 213. NIH Publication No. 82-1769. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1983). Carcinogenesis Bioassay of Diallyl Phthalate (CAS No. 131-17-9) in B6C3F$_1$ Mice (Gavage Study). Technical Report Series No. 242. NIH Publication No. 83-1798. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1984). Final report: Diethyl phthalate: Reproduction and fertility assessment in CD-1 mice when administered in the feed. National Toxicology Program and National Institute of Environmental Health Sciences.

National Toxicology Program (NTP) (1985). Toxicology and Carcinogenesis Studies of Diallylphthalate (CAS No. 131-17-9) in F344/N Rats (Gavage Studies). Technical Report Series No. 284. NIH Publication No. 85-2540. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1988). Developmental Toxicity Evaluation of Diethyl Phthalate (Cas No. 84-66-2) Administered to CD Rats on Gestational Days 6 Through 15. Final Report Prepared by Research Triangle Institute under NIEHS Contract No. N01-E5-55080; NTP-86-CTER-104.

National Toxicology Program (NTP) (1989). Developmental Toxicity Evaluation of Dimethyl Phthalate (Cas No. 131-11-3) Administered to CD Rats on Gestational Days 6 Through 15. Final Report Prepared by Research Triangle Institute under NIEHS Contract No. N01-E5-55080; NTP-86-CTER-105.

National Toxicology Program (NTP) (1994). Toxicity Studies of Dibutyl Phthalate (CAS No. 84-74-2) Administered in Feed to F334/N Rats and B6C3F$_1$ Mice. Toxicity Report Series No. 30. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Oishi, S., and Hiraga, K. (1980). Testicular atrophy induced by phthalic acid esters: effect on testosterone and zinc concentrations. *Toxicol. Appl. Pharmacol.* **53**, 35-41.

Oliwiecki, S., Beck, M.H., and Chalmers, R.J.G. (1991). Contact dermatitis from spectacle frames and hearing aid containing diethyl phthalate. *Contact Dermatitis* **25**, 264-265.

Omori, Y. (1976). Recent progress in safety evaluation studies on plasticizers and plastics and their controlled use in Japan. *Environ. Health Perspect.* **17**, 203-209.

Patty's Industrial Hygiene and Toxicology (1981). 3rd ed. (G.D. Clayton and F.E. Clayton, Eds.), Vol. 2A, pp. 2259-2412. John Wiley and Sons, New York.

Peterson, J.C., and Freeman, D.H. (1982). Phthalate ester concentration variations in dated sediment cores from the Chesapeake Bay. *Environ. Sci. Tech.* **16**, 464-469.

Plasterer, M.R., Bradshaw, W.S., Booth, G.M., Carter, M.W., Schuler, R.L., and Hardin, B.D. (1985). Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: Naphthalene, *p*-nitrophenyl, sodium selenite, dimethyl phthalate, ethylenethiourea, and four glycol ether derivatives. *J. Toxicol. Environ. Health* **15**, 25-38.

Rao, M.S., Subbarao, V., Yeldandi, A.V., and Reddy, J.K. (1992). Inhibition of spontaneous testicular Leydig cell tumor development in F-344 rats by dehydroepiandrosterone. *Cancer Lett.* **65**, 123-126.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia, PA.

Sax, N.I., Ed. (1984). *Dangerous Properties of Industrial Materials*, 6th ed. Van Nostrand Reinhold Company, New York.

Scott, R.C., Dugard, P.H., Ramsey, J.D., and Rhodes, C. (1987). *In vitro* absorption of some *o*-phthalate diesters through human and rat skin. *Environ. Health Perspect.* **74**, 223-227.

Seed, J.L. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. *Environ. Health Perspect.* **45**, 111-114.

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

Singh, A.R., Lawrence, W.H., and Autian, J. (1972). Teratogenicity of phthalate esters in rats. *J. Pharm. Sci.* **61**, 51-55.

Singh, A.R., Lawrence, W.H., and Autian, J. (1975). Maternal-fetal transfer of ^{14}C-di-2-ethylhexyl phthalate and ^{14}C-diethyl phthalate in rats. *J. Pharm. Sci.* **64**, 1347-1350.

Stanford Research Institute (SRI) Production (1991). Directory of chemical producers: United States of America. SRI International, 885. Menlo Park, CA

Staples, C.A., Werner, A.F., and Hoogheem, T.J. (1985). Assessment of priority pollutant concentrations in the United States using STORET database. *Environ. Toxicol. Chem.* **4**, 131-142.

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

Tanaka, C., Siratori, K., Ikegami, K., and Wakisaka, Y. (1987). A teratological evaluation following dermal application of diethyl phthalate to pregnant mice [in Japanese]. *Oyo Yakuri (Pharmacometrics)* **33**, 387-392.

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

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

U.S. Environmental Protection Agency (USEPA) (1980). Ambient Water Quality Criteria Document: Phthalate esters. (EPA-440/5-80-067), p. C12. U.S. Environmental Protection Agency, Washington, DC.

U.S. International Trade Commission (USITC) (1985). *Synthetic Organic Chemicals: United States Production and Sales, 1984.* USITC Publication 1745. U.S. Government Printing Office, Washington, DC.

van Nesselrooij, J.H.J., Kuper, C.F., and Bosland, M.C. (1992). Correlations between presence of spontaneous lesions of the pituitary (adenohypophysis) and plasma prolactin concentration in aged Wistar rats. *Vet. Pathol.* **29**, 288-300.

Walseth, F., Toftgård, R., and Nilsen, O.G. (1982). Phthalate esters I: Effects of cytochrome P-450 mediated metabolism in rat liver and lung, serum enzymatic activities and serum protein levels. *Arch. Toxicol.* **50**, 1-10.

Weast, R.C., Ed. (1986). *CRC Handbook of Chemistry and Physics*, 67th ed. CRC Press, Inc., Boca Raton, FL.

Weast, R.C., Ed. (1987). *CRC Handbook of Chemistry and Physics*, 68th ed. CRC Press, Inc., Boca Raton, FL.

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

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

Worthing, C.R., and Walker, S.B., Eds. (1987). *The Pesticide Manual. A World Compendium*, 8th ed. The British Crop Protection Council, Thornton Heath, UK.

Zeiger, E., Haworth, S., Mortelmans, K., and Speck, W. (1985). Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in *Salmonella*. *Environ. Mutagen.* **7**, 213-232.

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

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

TABLE A1	Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate	72
TABLE A2	Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate	76
TABLE A3	Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate	94
TABLE A4a	Historical Incidence of Pituitary Gland (Pars Distalis) Adenomas in Untreated Male F344/N Rats	97
TABLE A4b	Historical Incidence of Leukemia in Untreated Male F344/N Rats	98
TABLE A4c	Historical Incidence of Adenomas of the Testis in Untreated Male F344/N Rats	99
TABLE A5	Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate	100

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

	0 μL	100 μL	300 μL
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	9
Early deaths			
Moribund	31	38	26
Natural deaths	15	6	19
Survivors			
Died last week of study	1		
Terminal sacrifice	3	6	6
Animals examined microscopically	60	56	60
15-Month Interim Evaluation			
Endocrine System			
Adrenal gland, medulla	(10)		(9)
Pheochromocytoma benign	1 (10%)		
Islets, pancreatic	(1)		
Adenoma	1 (100%)		
Pituitary gland	(10)		(9)
Pars distalis, adenoma	4 (40%)		5 (56%)
Thyroid gland	(10)		(9)
C-cell, adenoma	1 (10%)		
Systems Examined With No Neoplasms Observed			
Alimentary System			
Cardiovascular System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Intestine large, colon	(41)	(47)	(44)
Adenocarcinoma			2 (5%)
Liver	(50)	(50)	(51)
Hepatocellular adenoma	1 (2%)		1 (2%)
Mesentery	(4)	(3)	(1)
Pancreas	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
Acinus, adenoma	1 (2%)		
Pharynx		(1)	
Papilloma		1 (100%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Alimentary System (continued)			
Salivary glands	(48)	(50)	(50)
Fibrosarcoma		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)
Papilloma squamous	2 (4%)	2 (4%)	3 (6%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(49)	(50)	(50)
Adenoma		1 (2%)	
Adrenal gland, medulla	(49)	(50)	(48)
Pheochromocytoma malignant		1 (2%)	1 (2%)
Pheochromocytoma benign	14 (29%)	8 (16%)	8 (17%)
Pheochromocytoma benign, multiple		1 (2%)	
Islets, pancreatic	(49)	(50)	(49)
Adenoma	6 (12%)	10 (20%)	7 (14%)
Adenoma, multiple		1 (2%)	
Carcinoma		1 (2%)	
Parathyroid gland	(47)	(49)	(48)
Carcinoma, metastatic			1 (2%)
Pituitary gland	(44)	(49)	(49)
Pars distalis, adenoma	39 (89%)	41 (84%)	41 (84%)
Pars distalis, carcinoma			1 (2%)
Thyroid gland	(48)	(50)	(48)
C-cell, adenoma	2 (4%)	2 (4%)	2 (4%)
C-cell, carcinoma		1 (2%)	2 (4%)
Follicular cell, adenoma	1 (2%)		
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)
General Body System			
Tissue NOS	(4)	(3)	(1)
Fibroma			1 (100%)
Fibrosarcoma	1 (25%)	1 (33%)	
Hemangiosarcoma	1 (25%)		
Genital System			
Epididymis	(48)	(48)	(50)
Preputial gland	(34)	(46)	(45)
Adenoma		1 (2%)	
Carcinoma	1 (3%)	1 (2%)	2 (4%)
Prostate	(48)	(50)	(49)
Seminal vesicle	(48)	(50)	(49)
Testes	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma			1 (2%)
Interstitial cell, adenoma	4 (8%)	3 (6%)	8 (16%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(49)	(49)	(48)
Lymph node	(50)	(50)	(50)
Mediastinal, carcinoma, metastatic		1 (2%)	
Lymph node, mandibular	(48)	(50)	(49)
Lymph node, mesenteric	(44)	(50)	(46)
Spleen	(50)	(50)	(50)
Sarcoma			1 (2%)
Thymus	(35)	(37)	(35)
Integumentary System			
Mammary gland	(44)	(38)	(43)
Fibroadenoma		1 (3%)	
Fibroma	2 (5%)	1 (3%)	
Sarcoma		1 (3%)	
Skin	(49)	(50)	(51)
Keratoacanthoma	1 (2%)	1 (2%)	
Face, papilloma			1 (2%)
Lip, papilloma			1 (2%)
Other, fibroma		1 (2%)	
Thoracic, keratoacanthoma			1 (2%)
Skin, control and site of application-no mass	(50)	(50)	(51)
Basal cell adenoma	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(51)
Alveolar/bronchiolar adenoma			1 (2%)
Carcinoma, metastatic		1 (2%)	
Nose	(50)	(50)	(49)
Adenoma			1 (2%)
Carcinoma, metastatic		1 (2%)	
Special Senses System			
Ear	(1)	(2)	(3)
Papilloma		1 (50%)	2 (67%)
Zymbal's gland		(3)	
Carcinoma		1 (33%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Urinary System			
Kidney	(50)	(50)	(51)
Lipoma	1 (2%)		
Renal tubule, adenoma	1 (2%)	1 (2%)	1 (2%)
Urethra	(1)		
Transitional epithelium, carcinoma	1 (100%)		
Urinary bladder	(48)	(50)	(47)
Carcinoma			1 (2%)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(51)
Leukemia mononuclear	9 (18%)	12 (24%)	13 (25%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Mesothelioma benign	2 (4%)		
Mesothelioma malignant		1 (2%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	6		5
2-Year study	46	49	50
Total primary neoplasms			
15-Month interim evaluation	7		5
2-Year study	95	101	104
Total animals with benign neoplasms			
15-Month interim evaluation	6		5
2-Year study	45	47	47
Total benign neoplasms			
15-Month interim evaluation	7		5
2-Year study	80	78	80
Total animals with malignant neoplasms			
2-Year study	17	21	23
Total malignant neoplasms			
2-Year study	17	23	24
Total animals with metastatic neoplasms			
2-Year study		1	1
Total metastatic neoplasms			
2-Year study		3	1

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL

Number of Days on Study	2 6 4	3 9 9	4 7 8	5 0 2	5 0 2	5 2 0	5 2 4	5 2 7	5 2 8	5 4 8	5 4 9	5 6 8	5 6 8	5 7 1	5 7 8	5 8 2	5 8 3	5 8 7	5 9 1	5 9 4	5 9 6	5 9 7	5 9 8	6 0 0	6 1 9
Carcass ID Number	0 2 6 1	0 3 8 1	0 2 1 1	0 3 4 1	0 5 3 1	0 5 1 1	0 5 7 1	0 3 0 1	0 1 1 1	0 5 2 1	0 4 9 1	0 2 2 1	0 4 3 1	0 1 9 1	0 1 2 1	0 2 8 1	0 2 4 1	0 2 9 1	0 5 9 1	0 5 6 1	0 2 5 1	0 1 8 1	0 4 7 1	0 2 7 1	0 1 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+	A	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery		+																		+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Stomach, glandular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																		+			+				+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X	X							X			X	X		X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X			X	X	X		X	X	X	X	X		X		X	X	X	X	X	X	X
Thyroid gland	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS	+									+															
Fibrosarcoma																									
Hemangiosarcoma																									

+: 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 Diethylphthalate: 0 μL (continued)

Number of Days on Study	6 2 2 6	6 2 9 9	6 2 9 9	6 3 6 6	6 3 6 6	6 4 4 4	6 4 6 6	6 5 1 1	6 5 2 2	6 6 8 8	6 7 1 1	6 7 3 3	6 7 4 4	6 8 0 0	6 8 1 1	6 8 7 7	6 9 1 1	6 9 9 9	7 0 2 2	7 0 9 9	7 3 0 0	7 3 4 4	7 3 4 4	7 3 4 5	
Carcass ID Number	0 3 2 1	0 3 7 1	0 4 1 1	0 4 2 1	0 5 0 1	0 1 4 1	0 5 5 1	0 4 0 1	0 3 9 1	0 4 4 1	0 5 8 1	0 1 5 1	0 4 5 1	0 3 6 1	0 6 0 1	0 3 3 1	0 3 1 1	0 4 8 1	0 1 7 1	0 1 6 1	0 3 5 1	0 2 0 1	0 2 3 1	0 4 6 1	0 5 4 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	40
Intestine large, colon	A	A	A	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	M	+	41
Intestine large, rectum	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																						X			1
Mesentery			+						+																4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma							X																		1
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma				X																					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																									
Blood vessel		+					+	+		+				+	+		+	+	+		+				13
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign	X							X				X		X	X	X		X					X	X	14
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X			X								X							X				X		6
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	44
Pars distalis, adenoma			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma															X										2
Follicular cell, adenoma							X																		1
Follicular cell, carcinoma																								X	1
General Body System																									
Tissue NOS				+																	+				4
Fibrosarcoma				X																					1
Hemangiosarcoma																					X				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	2 6 4	3 9 9	4 7 8	5 0 2	5 0 2	5 2 0	5 2 4	5 2 7	5 2 8	5 4 8	5 4 9	5 6 8	5 6 8	5 7 1	5 7 8	5 8 2	5 8 3	5 8 7	5 9 1	5 9 4	5 9 6	5 9 7	5 9 8	6 0 0	6 1 9
Carcass ID Number	0 2 6 1	0 3 8 1	0 2 1 1	0 3 4 1	0 5 3 1	0 5 1 1	0 5 7 1	0 3 0 1	0 1 1 1	0 5 2 1	0 4 9 1	0 2 2 1	0 4 3 1	0 1 9 1	0 1 2 1	0 2 8 1	0 2 4 1	0 5 9 1	0 5 9 1	0 5 6 1	0 2 5 1	0 1 8 1	0 4 7 1	0 2 7 1	0 1 3 1
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	
Penis																				+				+	
Preputial gland	+	+	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	+	+	+	M	+	+	
Carcinoma											X														
Prostate	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Interstitial cell, adenoma															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	M	+	+	I	M	+	+	M	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	I	M	+	+	+	M	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+
Fibroma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Astrocytoma malignant								X																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																									
Ear																									
Eye			+	+	+	+			+		+	+	+	+	+		+	+	+	+	+	+	+	+	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	6 2 6	6 2 9	6 2 9	6 3 6	6 3 6	6 4 4	6 4 6	6 5 1	6 5 2	6 6 8	6 7 1	6 7 3	6 7 4	6 8 0	6 8 1	6 8 7	6 9 1	6 9 9	7 0 2	7 0 9	7 3 0	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 3 2 1	0 3 7 1	0 4 1 1	0 4 2 1	0 5 0 1	0 1 4 1	0 5 5 1	0 4 0 1	0 3 9 1	0 4 4 1	0 5 8 1	0 1 5 1	0 4 5 1	0 3 6 1	0 6 0 1	0 3 3 1	0 3 1 1	0 4 8 1	0 1 7 1	0 1 6 1	0 3 5 1	0 2 0 1	0 2 3 1	0 4 6 1	0 5 4 1	Total Tissues/ Tumors
Genital System																									
Coagulating gland																			+						1
Epididymis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Penis										+						+					+	+			6
Preputial gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Carcinoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X						X												X			4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	M	+	M	M	+	+	+	35
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Fibroma														X											2
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																									1
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma															X										1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																					+				1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Ear																						+			1
Eye	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	2 6 4	3 9 9	4 7 8	5 0 2	5 0 2	5 2 0	5 2 4	5 2 7	5 2 8	5 4 8	5 4 9	5 6 8	5 6 8	5 7 1	5 7 8	5 8 2	5 8 3	5 8 7	5 9 1	5 9 4	5 9 6	5 9 7	5 9 8	6 0 0	6 1 9
Carcass ID Number	0 2 6 1	0 3 8 1	0 2 1 1	0 3 4 1	0 5 3 1	0 5 1 1	0 5 7 1	0 3 0 1	0 1 1 1	0 5 2 1	0 4 9 1	0 2 2 1	0 4 3 1	0 1 9 1	0 1 2 1	0 2 8 1	0 2 4 1	0 2 9 1	0 5 9 1	0 5 6 1	0 2 5 1	0 1 8 1	0 4 7 1	0 2 7 1	0 1 3 1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																							X		
Renal tubule, adenoma																									
Urethra																			+						
Transitional epithelium, carcinoma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X										X				X		X			
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic																									
Mesothelioma benign									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	6 2 6	6 2 9	6 2 9	6 3 6	6 3 6	6 4 4	6 4 6	6 5 1	6 5 2	6 6 8	6 7 1	6 7 3	6 7 4	6 8 0	6 8 1	6 8 7	6 9 1	6 9 9	7 0 2	7 0 9	7 3 0	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 3 2 1	0 3 7 1	0 4 1 1	0 4 2 1	0 5 0 1	0 1 4 1	0 5 5 1	0 4 0 1	0 3 9 1	0 4 4 1	0 5 8 1	0 1 5 1	0 4 5 1	0 3 6 1	0 6 0 1	0 3 3 1	0 3 1 1	0 4 8 1	0 1 7 1	0 1 6 1	0 3 5 1	0 2 0 1	0 2 3 1	0 4 6 1	0 5 4 1	Total Tissues/ Tumors
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma															X										1
Renal tubule, adenoma																									1
Urethra																									1
Transitional epithelium, carcinoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X			X				X						X		X	9
Lymphoma malignant histiocytic																									1
Lymphoma malignant lymphocytic																	X								1
Mesothelioma benign			X																						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL

Number of Days on Study	3 0 4	3 5 9	4 8 6	4 9 0	5 1 9	5 2 8	5 4 2	5 4 3	5 5 3	5 5 6	5 5 9	5 5 9	5 6 0	5 8 0	5 8 4	5 9 1	5 9 7	6 0 1	6 0 1	6 1 6	6 2 0	6 2 0	6 3 9	6 4 0	6 4 0
Carcass ID Number	1 3 4 1	1 3 5 1	1 5 3 1	1 6 4 1	1 5 9 1	1 7 0 1	1 6 2 1	1 5 5 1	1 4 7 1	1 5 0 1	1 4 6 1	1 6 1 1	1 6 8 1	1 3 1 1	1 5 6 1	1 5 7 1	1 6 9 1	1 3 6 1	1 5 2 1	1 4 4 1	1 3 3 1	1 4 3 1	1 7 4 1	1 7 7 1	1 7 9 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+							+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X							
Pharynx						+																			
Papilloma						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X	X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel																+		+	+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma benign																				X					
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X		X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	6 5 2	6 5 3	6 5 4	6 5 4	6 5 4	6 6 5	6 6 5	6 6 6	6 6 8	6 7 3	6 8 7	6 9 2	7 0 1	7 0 1	7 0 4	7 1 6	7 1 8	7 1 8	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	1 7 1 1	1 7 6 1	1 4 2 1	1 7 2 1	1 7 8 1	1 3 8 1	1 4 8 1	1 3 2 1	1 8 0 1	1 4 0 1	1 4 9 1	1 5 8 1	1 3 7 1	1 7 5 1	1 5 1 1	1 6 3 1	1 5 4 1	1 6 7 1	1 6 5 1	1 3 9 1	1 4 5 1	1 6 6 1	1 7 3 1	1 4 1 1	1 6 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+																			3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Pharynx																										1
Papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth											+															1
Cardiovascular System																										
Blood vessel			+					+					+			+		+							8
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign		X	X													X	X		X				X		X	8
Pheochromocytoma benign, multiple				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X			X		X			X	X								X		X		X			X	10
Adenoma, multiple																							X			1
Carcinoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X	X	X	X			X	X	X	X			X	X	X	X	X	X	X	X	X		41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X				X																2
C-cell, carcinoma	X																									1
Follicular cell, carcinoma														X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	3	3	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6
	0	5	8	9	1	2	4	4	5	5	5	5	6	8	8	9	9	0	0	1	2	2	3	4	4
	4	9	6	0	9	8	2	3	3	6	9	9	0	0	4	1	7	1	1	6	0	0	9	0	0
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	3	3	5	6	5	7	6	5	4	5	4	6	6	3	5	5	6	3	5	4	3	4	7	7	7
	4	5	3	4	9	0	2	5	7	0	6	1	8	1	6	7	9	6	2	4	3	3	4	7	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS	+															+									
Fibrosarcoma																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	I	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																	+								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	+	I	+	+	M	+	I	+	+	M	+	+	+	+	+	+	+	+	I	I	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+
Fibroadenoma																	X								
Fibroma																									
Sarcoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma									X																
Other, fibroma																									
Site of application-mass, adenoma																									
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	6 5 2	6 5 3	6 5 4	6 5 4	6 5 4	6 6 5	6 6 5	6 6 6	6 6 8	6 6 3	6 6 7	6 6 8	6 7 9	7 0 2	7 0 1	7 0 1	7 1 4	7 1 6	7 1 8	7 2 8	7 3 3	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	1 7 1 1	1 7 6 1	1 4 2 1	1 7 2 1	1 7 8 1	1 3 8 1	1 4 8 1	1 3 8 1	1 8 0 1	1 4 0 1	1 4 9 1	1 5 8 1	1 3 7 1	1 7 5 1	1 5 1 1	1 5 3 1	1 6 1 1	1 5 3 1	1 6 4 1	1 6 7 1	1 3 5 1	1 4 4 1	1 6 6 1	1 7 3 1	1 4 1 1	1 6 0 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																									+		3
Fibrosarcoma																									X		1
Genital System																											
Coagulating gland											+																1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Penis																	+										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										X	1
Carcinoma								X																			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma														X		X							X				3
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, carcinoma, metastatic									X																		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	I	M	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	37
Integumentary System																											
Mammary gland	+	+	M	+	+	+	+	M	+	M	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+		38
Fibroadenoma																											1
Fibroma																				X							1
Sarcoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																											1
Other, fibroma							X																				1
Site of application-mass, adenoma																										X	1
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle													+														1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	3 0 4	3 5 9	4 8 6	4 9 0	5 1 9	5 2 8	5 4 2	5 4 3	5 5 3	5 5 6	5 5 9	5 5 9	5 6 0	5 8 0	5 8 4	5 9 1	5 9 7	6 0 1	6 0 1	6 1 6	6 2 0	6 2 0	6 3 9	6 4 0	6 4 0
Carcass ID Number	1 3 4 1	1 3 5 1	1 5 3 1	1 6 4 1	1 5 9 1	1 7 0 1	1 6 2 1	1 5 5 1	1 4 7 1	1 5 0 1	1 4 6 1	1 6 1 1	1 6 8 1	1 3 1 1	1 5 6 1	1 5 7 1	1 6 9 1	1 3 6 1	1 5 2 1	1 4 4 1	1 3 3 1	1 4 3 1	1 7 4 1	1 7 7 1	1 7 9 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																					+				
Papilloma																									
Eye			+				+	+		+	+	+	+	+	+	+	+	+			+	+	+	+	+
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X											X						X			
Mesothelioma malignant	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	6 5 2	6 5 3	6 5 4	6 5 4	6 5 4	6 6 5	6 6 5	6 6 6	6 6 8	6 7 3	6 8 7	6 9 2	7 0 1	7 0 1	7 0 4	7 1 6	7 1 8	7 1 8	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	1 7 1 1	1 7 6 1	1 4 2 1	1 7 2 1	1 7 8 1	1 3 8 1	1 4 8 1	1 3 2 1	1 8 0 1	1 4 0 1	1 4 9 1	1 5 8 1	1 3 7 1	1 7 5 1	1 5 1 1	1 6 3 1	1 5 4 1	1 6 7 1	1 6 5 1	1 3 9 1	1 4 5 1	1 6 6 1	1 7 3 1	1 4 1 1	1 6 0 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear															+											2
Papilloma															X											1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Zymbal's gland		+							+																+	3
Carcinoma									X																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X									X		X			X			X	X	X	12
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	6 3 7	6 4 1	6 4 5	6 4 5	6 4 7	6 5 0	6 5 0	6 5 4	6 6 5	6 6 7	6 6 8	6 8 9	6 9 9	6 9 9	7 0 0	7 0 8	7 0 8	7 1 8	7 2 2	7 2 8	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 8 5 1	2 9 6 1	2 5 1 1	2 6 1 1	2 6 3 1	2 7 3 1	2 8 9 1	2 6 2 1	2 8 3 1	2 5 2 1	2 9 1 1	2 6 8 1	2 7 5 1	2 7 8 1	2 7 6 1	2 5 9 1	2 8 2 1	2 7 1 1	2 6 4 1	2 9 4 1	2 7 0 1	2 9 3 1	2 5 4 1	2 5 6 1	2 5 7 1	2 5 8 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma																X											2
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma		X																									1
Mesentery																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X													3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Blood vessel													+					+									2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																								X			1
Pheochromocytoma benign												X				X		X	X				X				8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X			X						X							X					X			7
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic										X																	1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X		X	X	X	X	X	X		X	X		X	X	X	X	X		X	X	X	X	X	41
Pars distalis, carcinoma																											1
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma																											2
C-cell, carcinoma						X																					2
Follicular cell, carcinoma										X																	1
General Body System																											
Tissue NOS																			+								1
Fibroma																			X								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6
	9	1	3	8	1	1	2	3	3	3	3	3	4	4	5	6	6	8	8	9	0	1	1	2	3
	1	3	7	6	2	9	8	3	4	4	5	8	2	9	9	2	3	0	2	6	7	2	5	6	2
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2
	9	5	5	9	8	7	8	6	8	9	9	6	7	6	5	6	0	9	7	6	8	9	8	7	8
	0	0	3	2	0	7	4	5	8	8	5	0	2	9	5	6	0	9	4	7	6	7	7	9	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																									
Epididymis	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+		+	+	+	M	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+
Carcinoma													X										X		
Prostate	+		+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Testes	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma						X																			
Hematopoietic System																									
Bone marrow	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A		A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma					X																				
Thymus	+		A	+	+	I	+	M	M	+	+	M	M	M	+	+	+	+	+	+	M	+	M	+	+
Integumentary System																									
Mammary gland	+		M	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Face, papilloma																									
Lip, papilloma					X																				
Thoracic, keratoacanthoma																									
Skin, control	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
Nervous System																									
Brain	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Trachea	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Papilloma																									
Eye						+		+	+		+			+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	6 3 7	6 4 1	6 4 5	6 4 5	6 4 7	6 5 0	6 5 0	6 5 4	6 6 5	6 6 7	6 6 8	6 8 9	6 9 9	6 9 9	6 7 0	7 0 8	7 0 8	7 1 8	7 2 2	7 2 8	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 8 5 1	2 9 6 1	2 5 1 1	2 6 1 1	2 6 3 1	2 7 3 1	2 8 9 1	2 6 2 1	2 8 3 1	2 5 2 1	2 9 1 1	2 6 8 1	2 7 5 1	2 7 8 1	2 7 6 1	2 5 9 1	2 8 2 1	2 7 1 1	2 6 4 1	2 9 4 1	2 7 0 1	2 9 3 1	2 5 4 1	2 5 6 1	2 5 7 1	2 5 8 1	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																		+					+			2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma																	X									1
Interstitial cell, adenoma	X													X				X	X				X	X	X	8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Thymus	+	+	+	+	+	+	M	+	I	M	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	35
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Face, papilloma															X											1
Lip, papilloma																										1
Thoracic, keratoacanthoma																									X	1
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																			X							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear			+																				+	+		3
Papilloma			X																				X			2
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	6 3 7	6 4 1	6 4 5	6 4 5	6 4 7	6 5 0	6 5 0	6 5 4	6 6 5	6 6 7	6 6 8	6 8 9	6 9 9	6 9 9	7 0 0	7 0 8	7 0 8	7 1 8	7 2 2	7 2 8	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 8 5 1	2 9 6 1	2 5 1 1	2 6 1 1	2 6 3 1	2 7 3 1	2 8 9 1	2 6 2 1	2 8 3 1	2 5 2 1	2 9 1 1	2 6 8 1	2 7 5 1	2 7 8 1	2 7 6 1	2 5 9 1	2 8 2 1	2 7 1 1	2 6 4 1	2 9 4 1	2 7 0 1	2 9 3 1	2 5 4 1	2 5 6 1	2 5 7 1	2 5 8 1	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, adenoma																								X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																									X		1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear							X			X					X					X	X					13

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

	0 μL	100 μL	300 μL
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	14/49 (29%)	9/50 (18%)	8/48 (17%)
Adjusted rate[b]	75.8%	61.3%	50.0%
Terminal rate[c]	2/4 (50%)	2/6 (33%)	1/6 (17%)
First incidence (days)	548	616	534
Life table test[d]	P=0.056N	P=0.052N	P=0.046N
Logistic regression test[d]	P=0.083N	P=0.093N	P=0.083N
Cochran-Armitage test[d]	P=0.130N		
Fisher exact test[d]		P=0.157N	P=0.123N
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	14/49 (29%)	10/50 (20%)	9/48 (19%)
Adjusted rate	75.8%	62.3%	60.0%
Terminal rate	2/4 (50%)	2/6 (33%)	2/6 (33%)
First incidence (days)	548	580	534
Life table test	P=0.084N	P=0.084N	P=0.067N
Logistic regression test	P=0.127N	P=0.150N	P=0.123N
Cochran-Armitage test	P=0.188N		
Fisher exact test		P=0.224N	P=0.185N
Pancreatic Islets: Adenoma			
Overall rate	6/49 (12%)	11/50 (22%)	7/49 (14%)
Adjusted rate	48.4%	78.0%	41.1%
Terminal rate	1/4 (25%)	4/6 (67%)	1/6 (17%)
First incidence (days)	571	620	533
Life table test	P=0.416N	P=0.343	P=0.562N
Logistic regression test	P=0.490N	P=0.248	P=0.565
Cochran-Armitage test	P=0.568		
Fisher exact test		P=0.154	P=0.500
Pancreatic Islets: Adenoma or Carcinoma			
Overall rate	6/49 (12%)	12/50 (24%)	7/49 (14%)
Adjusted rate	48.4%	80.2%	41.1%
Terminal rate	1/4 (25%)	4/6 (67%)	1/6 (17%)
First incidence (days)	571	620	533
Life table test	P=0.382N	P=0.287	P=0.562N
Logistic regression test	P=0.458N	P=0.181	P=0.565
Cochran-Armitage test	P=0.551N		
Fisher exact test		P=0.104	P=0.500
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	39/44 (89%)	41/49 (84%)	41/49 (84%)
Adjusted rate	100.0%	96.9%	100.0%
Terminal rate	3/3 (100%)	5/6 (83%)	5/5 (100%)
First incidence (days)	478	304	391
Life table test	P=0.371N	P=0.212N	P=0.318N
Logistic regression test	P=0.354N	P=0.348N	P=0.368N
Cochran-Armitage test	P=0.351N		
Fisher exact test		P=0.350N	P=0.350N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	39/44 (89%)	41/49 (84%)	42/49 (86%)
Adjusted rate	100.0%	96.9%	100.0%
Terminal rate	3/3 (100%)	5/6 (83%)	5/5 (100%)
First incidence (days)	478	304	391
Life table test	P=0.423N	P=0.212N	P=0.364N
Logistic regression test	P=0.473N	P=0.348N	P=0.478N
Cochran-Armitage test	P=0.470N		
Fisher exact test		P=0.350N	P=0.458N
Skin: Keratoacanthoma or Papilloma			
Overall rate	2/50 (4%)	1/50 (2%)	3/51 (6%)
Adjusted rate	12.3%	2.4%	25.2%
Terminal rate	0/4 (0%)	0/6 (0%)	1/6 (17%)
First incidence (days)	598	553	512
Life table test	P=0.436	P=0.437N	P=0.623
Logistic regression test	P=0.381	P=0.504N	P=0.527
Cochran-Armitage test	P=0.378		
Fisher exact test		P=0.500N	P=0.509
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	2/50 (4%)	2/50 (4%)	3/51 (6%)
Adjusted rate	7.6%	5.3%	11.8%
Terminal rate	0/4 (0%)	0/6 (0%)	0/6 (0%)
First incidence (days)	594	560	413
Life table test	P=0.447	P=0.659N	P=0.565
Logistic regression test	P=0.416	P=0.682	P=0.496
Cochran-Armitage test	P=0.428		
Fisher exact test		P=0.691N	P=0.509
Testes: Adenoma			
Overall rate	4/50 (8%)	3/50 (6%)	9/50 (18%)
Adjusted rate	34.7%	30.8%	69.1%
Terminal rate	1/4 (25%)	1/6 (17%)	3/6 (50%)
First incidence (days)	578	701	519
Life table test	P=0.124	P=0.319N	P=0.283
Logistic regression test	P=0.067	P=0.395N	P=0.164
Cochran-Armitage test	P=0.052		
Fisher exact test		P=0.500N	P=0.117
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	2/48 (4%)	3/50 (6%)	4/48 (8%)
Adjusted rate	12.6%	14.5%	12.8%
Terminal rate	0/4 (0%)	0/6 (0%)	0/6 (0%)
First incidence (days)	619	652	538
Life table test	P=0.318	P=0.606	P=0.385
Logistic regression test	P=0.287	P=0.551	P=0.330
Cochran-Armitage test	P=0.285		
Fisher exact test		P=0.520	P=0.339

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
All Organs: Mononuclear Cell Leukemia			
Overall rate	9/50 (18%)	12/50 (24%)	13/51 (25%)
Adjusted rate	65.1%	77.9%	53.4%
Terminal rate	2/4 (50%)	4/6 (67%)	1/6 (17%)
First incidence (days)	520	490	413
Life table test	P=0.381	P=0.579	P=0.393
Logistic regression test	P=0.260	P=0.381	P=0.256
Cochran-Armitage test	P=0.252		
Fisher exact test		P=0.312	P=0.252
All Organs: Benign Neoplasms			
Overall rate	45/50 (90%)	47/50 (94%)	47/51 (92%)
Adjusted rate	100.0%	100.0%	97.8%
Terminal rate	4/4 (100%)	6/6 (100%)	5/6 (83%)
First incidence (days)	478	304	391
Life table test	P=0.346N	P=0.211N	P=0.313N
Logistic regression test	P=0.517	P=0.400	P=0.532
Cochran-Armitage test	P=0.487		
Fisher exact test		P=0.357	P=0.487
All Organs: Malignant Neoplasms			
Overall rate	17/50 (34%)	21/50 (42%)	23/51 (45%)
Adjusted rate	89.5%	85.9%	79.4%
Terminal rate	3/4 (75%)	4/6 (67%)	3/6 (50%)
First incidence (days)	520	304	413
Life table test	P=0.353	P=0.522N	P=0.380
Logistic regression test	P=0.181	P=0.312	P=0.180
Cochran-Armitage test	P=0.177		
Fisher exact test		P=0.268	P=0.174
All Organs: Benign or Malignant Neoplasms			
Overall rate	46/50 (92%)	49/50 (98%)	50/51 (98%)
Adjusted rate	100.0%	100.0%	100.0%
Terminal rate	4/4 (100%)	6/6 (100%)	6/6 (100%)
First incidence (days)	478	304	391
Life table test	P=0.425N	P=0.243N	P=0.389N
Logistic regression test	P=0.176	P=0.183	P=0.197
Cochran-Armitage test	P=0.154		
Fisher exact test		P=0.181	P=0.175

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreatic islets, pituitary gland, skin, stomach, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the 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 controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE A4a
Historical Incidence of Pituitary Gland (Pars Distalis) Adenomas in Untreated Male F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence: Dermal (Acetone)	
Total	24/50 (48.0%)
Overall Historical Incidence: Feed	
Total	382/1,332 (28.7%)
Standard deviation	11.1%
Range	12%-60%
Overall Historical Incidence: Inhalation	
Total	226/390 (58.0%)
Standard deviation	8.9%
Range	45%-68%
Overall Historical Incidence: Water Gavage	
Total	116/363 (32%)
Standard deviation	7.7%
Range	24%-43%
Overall Historical Incidence: Corn Oil Gavage	
Total	344/1,046 (32.9%)
Standard deviation	9.1%
Range	18%-49%

[a] Data as of 31 March 1993

TABLE A4b
Historical Incidence of Leukemia in Untreated Male F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence: Dermal (Acetone)	
Total	16/50 (32.0%)
Overall Historical Incidence: Feed	
Total	661/1,353 (48.9%)
Standard deviation	8.8%
Range	32%-62%
Overall Historical Incidence: Inhalation	
Total	208/399 (52.1%)
Standard deviation	10.9%
Range	34%-66%
Overall Historical Incidence: Water Gavage	
Total	173/367 (47.1%)
Standard deviation	9.2%
Range	34%-56%
Overall Historical Incidence: Corn Oil Gavage	
Total	253/1,070 (23.6%)
Standard deviation	10.6%
Range	4%-46%

[a] Data as of 31 March 1993; includes data for lymphocytic, monocytic, mononuclear, or undifferentiated cell type leukemias

TABLE A4c
Historical Incidence of Adenomas of the Testis in Untreated Male F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence: Dermal (Acetone)	
Total	44/50 (88.0%)
Overall Historical Incidence: Feed	
Total	1,216/1,350 (90.1%)
Standard deviation	5.8%
Range	74%-98%
Overall Historical Incidence: Inhalation	
Total	270/399 (67.7%)
Standard deviation	7.8%
Range	58%-78%
Overall Historical Incidence: Water Gavage	
Total	313/366 (85.5%)
Standard deviation	6.7%
Range	73%-92%
Overall Historical Incidence: Corn Oil Gavage	
Total	933/1,062 (87.9%)
Standard deviation	5.8%
Range	76%-94%

[a] Data as of 31 March 1993

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate[a]

	0 μL	100 μL	300 μL
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	9
Early deaths			
Moribund	31	38	26
Natural deaths	15	6	19
Survivors			
Died last week of study	1		
Terminal sacrifice	3	6	6
Animals examined microscopically	60	56	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)		(9)
Degeneration, cystic, focal			1 (11%)
Degeneration, fatty, focal	1 (10%)		1 (11%)
Focal cellular change	1 (10%)		
Inflammation, granulomatous, focal	8 (80%)		7 (78%)
Bile duct, hyperplasia	10 (100%)		9 (100%)
Centrilobular, degeneration, fatty			1 (11%)
Pancreas	(10)		(9)
Acinus, atrophy	3 (30%)		3 (33%)
Acinus, hyperplasia, focal	1 (10%)		
Cardiovascular System			
Heart	(10)		(9)
Cardiomyopathy	8 (80%)		8 (89%)
Endocrine System			
Adrenal gland, cortex	(10)		(9)
Degeneration, fatty, focal	1 (10%)		
Hyperplasia, focal	1 (10%)		
Pituitary gland	(10)		(9)
Pigmentation, hemosiderin	1 (10%)		
Pars distalis, cyst	1 (10%)		
Pars distalis, hyperplasia, focal	2 (20%)		4 (44%)
General Body System			
Tissue NOS			(1)
Hemorrhage			1 (100%)
Inflammation, proliferative			1 (100%)

[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 Diethylphthalate (continued)

	0 μL	100 μL	300 μL
15-Month Interim Evaluation (continued)			
Genital System			
Preputial gland	(10)		(9)
Duct, inflammation, suppurative	1 (10%)		
Prostate	(10)		(9)
Hyperplasia, focal	1 (10%)		
Testes	(10)		(9)
Unilateral, atrophy			2 (22%)
Hematopoietic System			
Spleen	(10)		(9)
Pigmentation, hemosiderin	10 (100%)		9 (100%)
Integumentary System			
Mammary gland	(10)		(9)
Hyperplasia, cystic			1 (11%)
Duct, pigmentation	1 (10%)		
Skin	(10)	(6)	(9)
Other, inflammation, acute		1 (17%)	
Skin, control	(10)		(9)
Acanthosis	1 (10%)		
Skin, site of application-no mass	(10)	(5)	(9)
Acanthosis		5 (100%)	6 (67%)
Respiratory System			
Lung	(10)		(9)
Congestion	1 (10%)		
Nose	(10)		(9)
Fungus	1 (10%)		2 (22%)
Infiltration cellular, lymphocyte, diffuse	1 (10%)		
Infiltration cellular, mixed cell			1 (11%)
Nasolacrimal duct, exudate			1 (11%)
Nasolacrimal duct, inflammation, suppurative	1 (10%)		
Special Senses System			
Eye	(2)		
Cataract	1 (50%)		
Anterior chamber, hemorrhage	1 (50%)		
Retina, atrophy	2 (100%)		
Urinary System			
Kidney	(10)		(9)
Nephropathy	10 (100%)		9 (100%)
Pelvis, epithelium, hyperplasia	1 (10%)		1 (11%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
15-Month Interim Evaluation (continued)			
Systems Examined With No Lesions Observed			
Musculoskeletal System			
Nervous System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(49)	(50)
Hyperkeratosis	4 (8%)	3 (6%)	4 (8%)
Necrosis	1 (2%)		
Intestine large, cecum	(40)	(47)	(41)
Congestion	1 (3%)		
Edema	1 (3%)		1 (2%)
Ulcer			3 (7%)
Serosa, necrosis, focal	1 (3%)		
Intestine large, colon	(41)	(47)	(44)
Edema	1 (2%)		2 (5%)
Parasite metazoan	3 (7%)	1 (2%)	1 (2%)
Ulcer			1 (2%)
Muscularis, degeneration, focal	1 (2%)		
Muscularis, necrosis, focal		1 (2%)	
Serosa, necrosis, focal	1 (2%)		
Intestine small, duodenum	(47)	(49)	(47)
Ulcer			1 (2%)
Mucosa, erosion, focal	3 (6%)	2 (4%)	
Intestine small, ileum	(44)	(46)	(40)
Hemorrhage, focal	1 (2%)		
Mucosa, necrosis	1 (2%)		
Intestine small, jejunum	(42)	(46)	(40)
Intussusception	1 (2%)		
Liver	(50)	(50)	(51)
Angiectasis		1 (2%)	
Basophilic focus	1 (2%)		
Clear cell focus	4 (8%)		1 (2%)
Degeneration, cystic, focal	2 (4%)	3 (6%)	1 (2%)
Degeneration, fatty	26 (52%)	8 (16%)	4 (8%)
Eosinophilic focus	2 (4%)	1 (2%)	
Fibrosis, focal			2 (4%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic, focal	9 (18%)	11 (22%)	12 (24%)
Necrosis	1 (2%)	3 (6%)	6 (12%)
Bile duct, hyperplasia	43 (86%)	42 (84%)	38 (75%)
Hepatocyte, atrophy	1 (2%)		
Hepatocyte, hyperplasia, focal	2 (4%)		
Serosa, inflammation, necrotizing			1 (2%)
Mesentery	(4)	(3)	(1)
Fat, granuloma	2 (50%)	2 (67%)	1 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Alimentary System (continued)			
Pancreas	(50)	(50)	(50)
Accessory spleen	1 (2%)		
Cytoplasmic alteration, focal	1 (2%)	1 (2%)	1 (2%)
Edema			2 (4%)
Fibrosis	1 (2%)		
Acinus, atrophy	14 (28%)	17 (34%)	23 (46%)
Interlobular, inflammation, chronic		1 (2%)	
Salivary glands	(48)	(50)	(50)
Concretion			1 (2%)
Stomach	(49)	(50)	(50)
Muscularis, necrosis			1 (2%)
Muscularis, necrosis, focal	2 (4%)	3 (6%)	1 (2%)
Serosa, inflammation, necrotizing		1 (2%)	
Serosa, inflammation, suppurative			1 (2%)
Serosa, necrosis, focal		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)
Acanthosis	25 (51%)	21 (42%)	24 (48%)
Edema	13 (27%)	9 (18%)	10 (20%)
Hyperkeratosis	25 (51%)	20 (40%)	24 (48%)
Ulcer	13 (27%)	13 (26%)	8 (16%)
Muscularis, necrosis	2 (4%)		
Serosa, inflammation, suppurative		1 (2%)	
Serosa, inflammation, proliferative		1 (2%)	
Serosa, necrosis, focal	1 (2%)		
Stomach, glandular	(49)	(50)	(49)
Dilatation	1 (2%)		
Fibrosis		1 (2%)	
Foreign body	1 (2%)		
Epithelium, degeneration		1 (2%)	
Epithelium, hyperplasia		1 (2%)	
Mucosa, degeneration	11 (22%)	5 (10%)	4 (8%)
Mucosa, erosion, focal	1 (2%)	2 (4%)	1 (2%)
Muscularis, necrosis, focal	1 (2%)		
Tooth		(1)	
Inflammation, suppurative		1 (100%)	
Cardiovascular System			
Blood vessel	(13)	(8)	(2)
Degeneration	13 (100%)	7 (88%)	2 (100%)
Heart	(50)	(50)	(50)
Abscess	1 (2%)		
Cardiomyopathy	45 (90%)	44 (88%)	44 (88%)
Atrium, dilatation	1 (2%)		
Atrium, thrombus	6 (12%)	5 (10%)	3 (6%)
Myocardium, necrosis	1 (2%)		
Myocardium, necrosis, focal		1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Endocrine System			
Adrenal gland, cortex	(49)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	
Cytoplasmic alteration, focal		1 (2%)	
Degeneration	7 (14%)	3 (6%)	1 (2%)
Degeneration, fatty, focal	20 (41%)	21 (42%)	15 (30%)
Hyperplasia, focal	5 (10%)	9 (18%)	8 (16%)
Hypertrophy, focal			1 (2%)
Metaplasia, osseous, focal			1 (2%)
Adrenal gland, medulla	(49)	(50)	(48)
Hyperplasia, focal	21 (43%)	25 (50%)	14 (29%)
Islets, pancreatic	(49)	(50)	(49)
Hyperplasia	1 (2%)		2 (4%)
Parathyroid gland	(47)	(49)	(48)
Hyperplasia, focal	1 (2%)		1 (2%)
Hypertrophy	32 (68%)	30 (61%)	19 (40%)
Pituitary gland	(44)	(49)	(49)
Angiectasis		1 (2%)	1 (2%)
Cyst		2 (4%)	
Hemorrhage			2 (4%)
Pigmentation	1 (2%)		1 (2%)
Pars distalis, cyst			1 (2%)
Pars distalis, hyperplasia, focal	2 (5%)	3 (6%)	6 (12%)
Thyroid gland	(48)	(50)	(48)
C-cell, hyperplasia	7 (15%)	7 (14%)	8 (17%)
Follicular cell, hyperplasia	1 (2%)		
General Body System			
Tissue NOS	(4)	(3)	(1)
Inflammation, suppurative	1 (25%)		
Genital System			
Coagulating gland	(1)	(1)	
Inflammation	1 (100%)		
Inflammation, suppurative		1 (100%)	
Epididymis	(48)	(48)	(50)
Degeneration, focal	35 (73%)	38 (79%)	31 (62%)
Fibrosis	20 (42%)	20 (42%)	11 (22%)
Penis	(6)	(2)	(2)
Inflammation, acute	3 (50%)	2 (100%)	
Thrombus	1 (17%)		
Preputial gland	(34)	(46)	(45)
Abscess	2 (6%)	1 (2%)	2 (4%)
Abscess, acute		1 (2%)	
Ectasia	4 (12%)	1 (2%)	4 (9%)
Fibrosis	21 (62%)	23 (50%)	24 (53%)
Hyperplasia			1 (2%)
Inflammation, chronic		5 (11%)	3 (7%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Genital System (continued)			
Prostate	(48)	(50)	(49)
Cyst			1 (2%)
Hyperplasia, focal			3 (6%)
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative	29 (60%)	25 (50%)	27 (55%)
Seminal vesicle	(48)	(50)	(49)
Atrophy	15 (31%)	13 (26%)	12 (24%)
Depletion	17 (35%)	21 (42%)	10 (20%)
Hyperplasia	1 (2%)		
Inflammation, suppurative	2 (4%)	4 (8%)	1 (2%)
Testes	(50)	(50)	(50)
Hypoplasia	1 (2%)	1 (2%)	1 (2%)
Polyarteritis	3 (6%)	4 (8%)	4 (8%)
Interstitial cell, hyperplasia	4 (8%)	1 (2%)	3 (6%)
Seminiferous tubule, atrophy	23 (46%)	31 (62%)	20 (40%)
Seminiferous tubule, degeneration	14 (28%)	8 (16%)	8 (16%)
Hematopoietic System			
Bone marrow	(49)	(49)	(48)
Hypoplasia	6 (12%)	6 (12%)	3 (6%)
Lymph node	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Mediastinal, angiectasis		2 (4%)	
Mediastinal, hemorrhage	2 (4%)		1 (2%)
Lymph node, mandibular	(48)	(50)	(49)
Hyperplasia		1 (2%)	
Lymph node, mesenteric	(44)	(50)	(46)
Angiectasis		1 (2%)	
Congestion		1 (2%)	
Hemorrhage	3 (7%)	1 (2%)	
Inflammation, granulomatous			1 (2%)
Spleen	(50)	(50)	(50)
Congestion	3 (6%)		3 (6%)
Depletion lymphoid	1 (2%)		
Fibrosis	4 (8%)	4 (8%)	4 (8%)
Hematopoietic cell proliferation	8 (16%)	9 (18%)	7 (14%)
Infarct		1 (2%)	2 (4%)
Pigmentation, hemosiderin	16 (32%)	14 (28%)	14 (28%)
Capsule, hyperplasia		1 (2%)	
Capsule, hyperplasia, focal		1 (2%)	
Thymus	(35)	(37)	(35)
Depletion lymphoid	5 (14%)	4 (11%)	7 (20%)
Hemorrhage	1 (3%)		
Hyperplasia, pseudoepitheliomatous		2 (5%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Integumentary System			
Mammary gland	(44)	(38)	(43)
Abscess	1 (2%)		
Galactocele		1 (3%)	
Hyperplasia	1 (2%)	3 (8%)	2 (5%)
Lactation	39 (89%)	37 (97%)	40 (93%)
Duct, ectasia	1 (2%)		
Skin	(49)	(50)	(51)
Abdominal, edema		1 (2%)	
Abdominal, exudate		1 (2%)	
Abdominal, inflammation, suppurative	1 (2%)		
Abdominal, subcutaneous tissue, edema			1 (2%)
Foot, hemorrhage		1 (2%)	
Other, cyst epithelial inclusion	1 (2%)		
Other, inflammation, suppurative	3 (6%)		1 (2%)
Prepuce, hyperkeratosis	1 (2%)		
Prepuce, inflammation	1 (2%)		
Skin, control	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)	
Skin, site of application-no mass	(50)	(50)	(51)
Acanthosis	2 (4%)	5 (10%)	21 (41%)
Cyst epithelial inclusion	3 (6%)		
Exudate		1 (2%)	
Hyperkeratosis			2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)
Proliferation connective tissue	1 (2%)	1 (2%)	
Musculoskeletal System			
Bone	(49)	(49)	(49)
Fibrous osteodystrophy	22 (45%)	19 (39%)	11 (22%)
Hyperostosis		1 (2%)	1 (2%)
Hypoplasia	1 (2%)		
Skeletal muscle	(1)	(1)	(1)
Degeneration, focal	1 (100%)		
Diaphragm, inflammation, proliferative			1 (100%)
Diaphragm, necrosis, focal		1 (100%)	
Nervous System			
Brain	(50)	(50)	(50)
Compression	5 (10%)	8 (16%)	9 (18%)
Hemorrhage	1 (2%)		1 (2%)
Hydrocephalus		1 (2%)	1 (2%)
Infarct		1 (2%)	
Inflammation, chronic, focal	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(51)
Atelectasis	2 (4%)	1 (2%)	
Congestion	17 (34%)	13 (26%)	18 (35%)
Edema			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, histiocyte	1 (2%)	3 (6%)	1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic	22 (44%)	14 (28%)	11 (22%)
Alveolar epithelium, hyperplasia			1 (2%)
Alveolar epithelium, hyperplasia, focal		1 (2%)	
Nose	(50)	(50)	(49)
Exudate		1 (2%)	
Fibrosis, focal		1 (2%)	
Foreign body	3 (6%)	5 (10%)	
Fungus	3 (6%)	4 (8%)	5 (10%)
Inflammation, chronic	4 (8%)	5 (10%)	5 (10%)
Inflammation, suppurative	7 (14%)	2 (4%)	7 (14%)
Nasolacrimal duct, inflammation, chronic			1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)
Submucosa, olfactory epithelium, glands, hypertrophy			1 (2%)
Special Senses System			
Ear	(1)	(2)	(3)
Hyperkeratosis	1 (100%)		
Ulcer			1 (33%)
Eye	(43)	(43)	(42)
Cataract	42 (98%)	43 (100%)	42 (100%)
Hemorrhage	4 (9%)	4 (9%)	1 (2%)
Synechia	1 (2%)		
Anterior chamber, inflammation, suppurative		1 (2%)	1 (2%)
Cornea, inflammation	5 (12%)	4 (9%)	
Retina, atrophy	34 (79%)	35 (81%)	34 (81%)
Zymbal's gland		(3)	
Abscess		2 (67%)	
Urinary System			
Kidney	(50)	(50)	(51)
Inflammation, suppurative	1 (2%)		
Nephropathy	50 (100%)	50 (100%)	51 (100%)
Pelvis, dilatation	1 (2%)	2 (4%)	
Pelvis, epithelium, hyperplasia	29 (58%)	28 (56%)	21 (41%)
Pelvis, epithelium, inflammation	1 (2%)		
Pelvis, epithelium, mineralization		2 (4%)	1 (2%)
Renal tubule, mineralization	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Urinary System (continued)			
Urinary bladder	(48)	(50)	(47)
Hemorrhage	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, suppurative	1 (2%)		
Necrosis	1 (2%)		
Mucosa, hyperplasia	2 (4%)		1 (2%)

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

TABLE B1	Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate	110
TABLE B2	Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate	114
TABLE B3	Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate	132
TABLE B4a	Historical Incidence of Pituitary Gland (Pars Distalis) Adenomas in Untreated Female F344/N Rats	138
TABLE B4b	Historical Incidence of Mammary Gland Fibroadenomas in Untreated Female F344/N Rats	139
TABLE B5	Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate	140

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

	0 µL	100 µL	300 µL
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	9	10	10
Early deaths			
Moribund	12	12	17
Natural deaths	9	10	10
Survivors			
Died last week of study			2
Terminal sacrifice	30	28	21
Animals examined microscopically	60	52	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(9)	(2)	(10)
Leukemia mononuclear	1 (11%)		1 (10%)
Endocrine System			
Pituitary gland	(9)	(1)	(10)
Pars distalis, adenoma	4 (44%)		2 (20%)
Hematopoietic System			
Spleen	(9)	(2)	(10)
Leukemia mononuclear	1 (11%)		1 (10%)
Integumentary System			
Mammary gland	(9)	(1)	(10)
Fibroadenoma	2 (22%)		
Systemic Lesions			
Multiple organs[b]	(9)	(2)	(10)
Leukemia mononuclear	1 (11%)		1 (10%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
General Body System			
Genital System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
Urinary System			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study			
Alimentary System			
Intestine large, colon	(49)	(47)	(48)
Liver	(50)	(50)	(50)
Hepatocellular adenoma	1 (2%)	1 (2%)	
Mesentery	(3)	(3)	(1)
Pancreas	(50)	(50)	(50)
Adenoma			1 (2%)
Salivary glands	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous			1 (2%)
Stomach, glandular	(50)	(50)	(50)
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(51)	(50)	(50)
Adenoma	4 (8%)	4 (8%)	6 (12%)
Adenoma, multiple			1 (2%)
Adrenal gland, medulla	(49)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	
Pheochromocytoma benign	3 (6%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	3 (6%)
Carcinoma	2 (4%)	3 (6%)	
Parathyroid gland	(45)	(50)	(47)
Adenoma			1 (2%)
Pituitary gland	(50)	(49)	(48)
Pars distalis, adenoma	38 (76%)	33 (67%)	33 (69%)
Pars distalis, carcinoma	2 (4%)	2 (4%)	1 (2%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Adenoma	1 (2%)		
C-cell, adenoma			1 (2%)
C-cell, carcinoma	6 (12%)	5 (10%)	2 (4%)
Follicular cell, carcinoma	3 (6%)	1 (2%)	1 (2%)
General Body System			
Tissue NOS	(2)	(2)	(2)
Basosquamous tumor malignant		1 (50%)	
Fibrosarcoma	1 (50%)		
Sarcoma			1 (50%)
Genital System			
Clitoral gland	(44)	(39)	(40)
Adenoma	5 (11%)		2 (5%)
Carcinoma	2 (5%)	1 (3%)	2 (5%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Genital System (continued)			
Ovary	(50)	(50)	(50)
Carcinoma			1 (2%)
Uterus	(50)	(50)	(50)
Leiomyoma			1 (2%)
Polyp stromal	2 (4%)	3 (6%)	6 (12%)
Sarcoma stromal			1 (2%)
Schwannoma malignant	1 (2%)		1 (2%)
Hematopoietic System			
Lymph node	(50)	(50)	(50)
Lymph node, mandibular	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)
Spleen	(51)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Thymus	(44)	(43)	(42)
Integumentary System			
Mammary gland	(50)	(48)	(50)
Adenocarcinoma	5 (10%)	3 (6%)	3 (6%)
Adenoma	1 (2%)		
Fibroadenoma	20 (40%)	11 (23%)	7 (14%)
Fibroadenoma, multiple	1 (2%)	1 (2%)	
Fibroma			1 (2%)
Musculoskeletal System			
Bone	(48)	(49)	(50)
Osteosarcoma	1 (2%)		
Nervous System			
Brain	(50)	(50)	(50)
Carcinoma, metastatic	1 (2%)	2 (4%)	
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)		
Trachea	(50)	(50)	(50)
Special Senses System			
Zymbal's gland	(1)	(1)	(1)
Carcinoma		1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Urinary System			
Kidney	(51)	(50)	(50)
Carcinoma		1 (2%)	
Urinary bladder	(48)	(47)	(49)
Papilloma	1 (2%)		1 (2%)
Systemic Lesions			
Multiple organs	(51)	(50)	(50)
Leukemia monocytic	1 (2%)		
Leukemia mononuclear	17 (33%)	15 (30%)	16 (32%)
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	7		3
2-Year study	51	48	46
Total primary neoplasms			
15-Month interim evaluation	7		3
2-Year study	126	90	95
Total animals with benign neoplasms			
15-Month interim evaluation	6		2
2-Year study	47	41	39
Total benign neoplasms			
15-Month interim evaluation	6		2
2-Year study	82	55	66
Total animals with malignant neoplasms			
15-Month interim evaluation	1		1
2-Year study	32	27	23
Total malignant neoplasms			
15-Month interim evaluation	1		1
2-Year study	44	35	29
Total animals with metastatic neoplasms			
2-Year study	1	2	
Total metastatic neoplasms			
2-Year study	1	2	

[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 Diethylphthalate: 0 μL

Number of Days on Study	3 3 1	4 5 8	4 6 5	5 5 1	5 5 2	5 5 5	5 6 2	5 6 9	5 6 9	5 9 3	6 1 2	6 5 0	6 5 5	6 5 6	6 7 9	6 8 3	7 0 5	7 1 7	7 2 4	7 3 0	7 3 1	7 3 4	7 3 4	7 3 4
Carcass ID Number	0 6 5 1	1 0 3 1	1 1 7 1	1 0 7 1	0 7 6 1	1 0 2 1	1 0 8 1	0 8 9 1	0 9 3 1	0 7 5 1	0 2 0 1	0 8 1 1	0 8 3 1	1 1 9 1	0 7 7 1	1 1 5 1	0 8 2 1	0 7 4 1	0 9 8 1	1 1 6 1	1 0 9 1	0 7 1 1	0 7 2 1	0 7 3 1	0 7 8 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X
Mesentery			+				+											+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign																								
Islets, pancreatic		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X									
Carcinoma																					X			
Parathyroid gland		M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X		X		X	X	X	X	X	X		X	X		X			X	X	X	X
Pars distalis, carcinoma															X					X				
Pars intermedia, adenoma																								
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
C-cell, carcinoma														X								X		
Follicular cell, carcinoma			X		X																			
General Body System																								
Tissue NOS		+																						
Fibrosarcoma																								

+: 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 Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 7 9 1	0 8 0 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 7 1	0 8 8 1	0 9 0 1	0 9 1 1	0 9 2 1	0 9 4 1	0 9 5 1	0 9 6 1	0 9 7 1	0 9 9 1	0 9 0 1	1 0 1 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 8 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 3 1	1 1 4 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																											1
Mesentery																											3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma										X			X													X	4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																		X									1
Pheochromocytoma benign								X							X		X										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X							X																			3
Carcinoma																			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	X		X	X	X	X	X	X	38
Pars distalis, carcinoma																											2
Pars intermedia, adenoma								X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																							1
C-cell, carcinoma						X	X	X												X							6
Follicular cell, carcinoma					X																						3
General Body System																											
Tissue NOS										+																	2
Fibrosarcoma										X																	1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	3	5	6	5	5	5	6	6	6	9	1	5	5	5	7	8	0	1	2	3	3	3	3	3
	1	8	5	1	2	5	2	9	9	3	2	0	5	6	9	3	5	7	4	0	1	4	4	4
Carcass ID Number	0	1	1	1	0	1	1	0	0	0	1	0	0	1	0	1	0	0	0	1	1	0	0	0
	6	0	1	0	7	0	0	8	9	7	2	8	8	1	7	1	8	7	9	1	0	7	7	7
	5	3	7	7	6	2	8	9	3	5	0	1	3	9	7	5	2	4	8	6	9	1	2	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																								
Clitoral gland		+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma												X						X					X	
Carcinoma																								
Ovary		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																								X
Schwannoma malignant																						X		
Vagina												+												
Hematopoietic System																								
Bone marrow		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus		+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	I	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenocarcinoma			X																					X
Adenoma																				X				
Fibroadenoma	X					X			X									X				X		
Fibroadenoma, multiple											X													
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								
Nervous System																								
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic															X									
Respiratory System																								
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Eye	+			+		+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 7 9 1	0 8 0 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 7 1	0 8 8 1	0 9 0 1	0 9 1 1	0 9 2 1	0 9 4 1	0 9 5 1	0 9 6 1	0 9 7 1	0 9 9 1	0 9 0 1	1 0 1 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 8 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 3 1	1 1 4 1	Total Tissues/ Tumors
Genital System																											
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma										X									X								5
Carcinoma															X						X						2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X																				2
Schwannoma malignant																											1
Vagina																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																X					X	5
Adenoma																											1
Fibroadenoma	X		X			X		X	X	X				X		X	X			X	X	X	X		X	X	20
Fibroadenoma, multiple																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarcoma								X																			1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																								1
Alveolar/bronchiolar carcinoma														X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear				+																							1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Zymbal's gland		+																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	3	5	6	5	5	5	6	6	6	9	1	5	5	5	7	8	0	1	2	3	3	3	3	3	3	
	1	8	5	1	2	5	2	9	9	3	2	0	5	6	9	3	5	7	4	0	1	4	4	4	4	
Carcass ID Number	0	1	1	1	0	1	1	0	0	0	1	0	0	1	0	1	0	0	0	1	1	0	0	0	0	
	6	0	1	0	7	0	0	8	9	7	2	8	8	1	7	1	8	7	9	1	0	7	7	7	7	
	5	3	7	7	6	2	8	9	3	5	0	1	3	9	7	5	2	4	8	6	9	1	2	3	8	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	
Papilloma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia monocytic				X																						
Leukemia mononuclear		X		X		X		X	X	X		X			X	X		X			X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 7 9 1	0 8 0 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 7 1	0 8 8 1	0 9 0 1	0 9 1 1	0 9 2 1	0 9 4 1	0 9 5 1	0 9 6 1	0 9 7 1	0 9 9 1	0 9 0 1	1 0 1 1	1 0 4 1	1 0 5 1	1 0 6 1	1 1 8 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 3 1	1 1 4 1	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma																									X		1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia monocytic																											1
Leukemia mononuclear										X	X		X	X	X						X						17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 3 0 1	1 9 2 1	1 9 5 1	1 9 7 1	1 9 8 1	2 0 0 1	2 0 1 1	2 0 2 1	2 0 6 1	2 0 7 1	2 0 8 1	2 0 8 1	2 1 9 1	2 2 0 1	2 2 1 1	2 2 2 1	2 2 4 1	2 2 5 1	2 2 7 1	2 2 8 1	2 3 3 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																					X					1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																X	4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Carcinoma			X			X					X															3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X		X	X	X		X	X		X	X	X	X			X	X	X		X	X		33
Pars distalis, carcinoma																	X									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma				X													X			X						5
Follicular cell, carcinoma														X												1
General Body System																										
Tissue NOS																										2
Basosquamous tumor malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	4 1 9	4 3 4	4 9 4	5 4 5	5 5 1	5 5 5	5 6 7	5 6 8	5 7 3	5 7 4	6 0 0	6 4 0	6 4 5	6 5 0	6 5 4	6 5 5	6 5 9	6 7 3	6 7 5	6 8 7	7 1 3	7 3 3	7 3 4	7 3 4
Carcass ID Number	1 9 4 1	2 1 4 1	2 1 1 1	2 1 5 1	2 3 2 1	2 3 4 1	1 9 1 1	1 9 6 1	2 0 3 1	2 3 5 1	2 4 0 1	2 0 0 1	1 9 5 1	2 2 9 1	1 9 3 1	2 2 3 1	2 0 6 1	2 1 4 1	2 1 0 1	2 0 7 1	2 1 9 1	2 1 2 1	2 1 3 1	2 1 6 1	2 2 9 1
Genital System																									
Clitoral gland	M	M	M	M	+	+	M	M	M	M	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X					X						X	
Fibroadenoma														X			X	X							
Fibroadenoma, multiple																				X					
Skin	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic									X																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye			+				+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 3 0 1	1 9 2 1	1 9 5 1	1 9 7 1	1 9 8 1	2 0 0 1	2 0 1 1	2 0 2 1	2 0 6 1	2 0 7 1	2 0 8 1	2 0 8 1	2 1 1 1	2 1 9 1	2 2 0 1	2 2 1 1	2 2 2 1	2 2 4 1	2 2 5 1	2 2 7 1	2 2 8 1	2 3 3 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Carcinoma								X																		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal									X										X				X			3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Thymus	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										3
Fibroadenoma						X		X		X							X	X				X	X	X		11
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic																	X									2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear	+																									1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Zymbal's gland	+																									1
Carcinoma	X																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 100 μL (continued)

Number of Days on Study	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 3 0 1	1 9 2 1	1 9 5 1	1 9 7 1	1 9 8 1	2 0 0 1	2 0 1 1	2 0 2 1	2 0 6 1	2 0 7 1	2 0 8 1	2 0 8 1	2 1 8 1	2 1 9 1	2 2 0 1	2 2 1 1	2 2 2 1	2 2 4 1	2 2 5 1	2 2 7 1	2 2 8 1	2 3 3 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Urinary bladder	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	47
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X			X			X		X							X		X				15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL

Number of Days on Study	3 4 4	3 6 7	4 3 0	4 8 9	5 2 0	5 4 1	5 4 3	5 4 9	5 5 9	5 6 9	5 8 4	5 8 5	5 8 8	5 9 1	5 9 5	6 1 1	6 2 6	6 3 8	6 3 9	6 5 7	6 5 8	6 7 5	6 8 0	6 8 7	6 8 9
Carcass ID Number	3 4 7 1	3 2 1 1	3 5 5 1	3 4 6 1	3 2 5 1	3 5 4 1	3 2 4 1	3 5 8 1	3 3 1 1	3 1 3 1	3 1 6 1	3 2 0 1	3 5 1 1	3 1 5 1	3 1 4 1	3 5 6 1	3 1 1 1	3 2 6 1	3 2 8 1	3 2 3 1	3 3 2 1	3 4 1 1	3 5 0 1	3 5 2 1	3 1 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	+	+	A	+	A	A	+	+	A	+	+	+	+	+	A	A	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth									+																
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X													X		X	
Adenoma, multiple																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X				X		X	X	X	X	X	X				X		X		X	X		
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																						X			
Follicular cell, carcinoma										X															
General Body System																									
Tissue NOS					+								+												
Sarcoma													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	7 0 6	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 3 4 1	3 6 0 1	3 1 7 1	3 1 9 1	3 2 2 1	3 3 7 1	3 3 8 1	3 3 9 1	3 4 0 1	3 4 2 1	3 4 3 1	3 4 4 1	3 4 5 1	3 4 8 1	3 4 9 1	3 4 5 1	3 5 3 1	3 1 2 1	3 2 7 1	3 2 9 1	3 3 0 1	3 3 3 1	3 3 5 1	3 3 6 1	3 5 7 1	3 5 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																								+		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X										X			X								6
Adenoma, multiple																					X					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X															X		X	3
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	33
Pars distalis, carcinoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X				1
C-cell, carcinoma																					X					2
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS																										2
Sarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	3 4 4	3 6 7	4 3 0	4 8 9	5 2 0	5 4 1	5 4 3	5 4 9	5 5 9	5 6 9	5 8 4	5 8 5	5 8 8	5 9 1	5 9 5	6 1 1	6 2 6	6 3 8	6 3 9	6 5 7	6 5 8	6 7 5	6 8 0	6 8 7	6 8 9
Carcass ID Number	3 4 7 1	3 2 1 1	3 5 5 1	3 4 6 1	3 2 5 1	3 5 4 1	3 2 4 1	3 5 8 1	3 3 1 1	3 1 3 1	3 1 6 1	3 2 0 1	3 5 1 1	3 1 5 1	3 1 4 1	3 5 6 1	3 1 1 1	3 2 6 1	3 2 8 1	3 2 3 1	3 3 2 1	3 4 1 1	3 5 0 1	3 5 2 1	3 1 8 1
Genital System																									
Clitoral gland	+	+	+	+	M	+	M	+	M	M	+	+	+	M	M	M	+	+	+	M	M	+	M	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																				X					
Polyp stromal		X																					X		
Sarcoma stromal					X																				
Schwannoma malignant										X															
Vagina																			+						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma												X				X					X				
Fibroma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+						+			+				+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland	+																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	7 0 6	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 3 4 1	3 6 0 1	1 7 1	1 9 1	2 2 1	3 7 1	3 8 1	3 9 1	4 0 1	4 2 1	4 3 1	4 4 1	4 5 1	4 8 1	4 9 1	5 3 1	1 2 1	2 7 1	2 9 1	3 0 1	3 3 1	3 5 1	5 6 1	5 7 1	5 9 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma									X											X						2
Carcinoma											X												X			2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal										X								X				X	X			6
Sarcoma stromal																										1
Schwannoma malignant																										1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X										X						X					3
Fibroadenoma						X				X		X													X	7
Fibroma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Zymbal's gland																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diethylphthalate: 300 μL (continued)

Number of Days on Study	7 0 6	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 3 4 1	3 6 0 1	3 1 7 1	3 1 9 1	3 2 2 1	3 3 7 1	3 3 8 1	3 3 9 1	3 4 0 1	3 4 2 1	3 4 3 1	3 4 4 1	3 4 5 1	3 4 8 1	3 4 9 1	3 5 3 1	3 1 2 1	3 2 7 1	3 2 9 1	3 3 0 1	3 3 3 1	3 3 5 1	3 3 6 1	5 5 7 1	5 5 9 1	Total Tissues/ Tumors
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma																									1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X						X	X	X										X	X				16

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

	0 µL	100 µL	300 µL
Adrenal Cortex: Adenoma			
Overall rate[a]	4/51 (8%)	4/50 (8%)	7/50 (14%)
Adjusted rate[b]	12.8%	12.7%	25.0%
Terminal rate[c]	3/30 (10%)	3/28 (11%)	4/23 (17%)
First incidence (days)	730	567	559
Life table test[d]	P=0.099	P=0.607	P=0.143
Logistic regression test[d]	P=0.129	P=0.610	P=0.173
Cochran-Armitage test[d]	P=0.184		
Fisher exact test[d]		P=0.631	P=0.251
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	10.0%	3.6%	4.3%
Terminal rate	3/30 (10%)	1/28 (4%)	1/23 (4%)
First incidence (days)	734 (T)	734 (T)	734 (T)
Life table test	P=0.354N	P=0.329N	P=0.403N
Logistic regression test	P=0.354N	P=0.329N	P=0.403N
Cochran-Armitage test	P=0.272N		
Fisher exact test		P=0.309N	P=0.309N
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	13.3%	5.7%	4.3%
Terminal rate	4/30 (13%)	1/28 (4%)	1/23 (4%)
First incidence (days)	734 (T)	551	734 (T)
Life table test	P=0.217N	P=0.367N	P=0.265N
Logistic regression test	P=0.189N	P=0.355N	P=0.265N
Cochran-Armitage test	P=0.151N		
Fisher exact test		P=0.339N	P=0.181N
Clitoral Gland: Adenoma			
Overall rate	5/44 (11%)	0/39 (0%)	2/40 (5%)
Adjusted rate	15.2%	0.0%	8.7%
Terminal rate	3/29 (10%)	0/28 (0%)	2/23 (9%)
First incidence (days)	650	–[e]	734 (T)
Life table test	P=0.325N	P=0.042N	P=0.330N
Logistic regression test	P=0.309N	P=0.042N	P=0.312N
Cochran-Armitage test	P=0.263N		
Fisher exact test		P=0.037N	P=0.258N
Clitoral Gland: Carcinoma			
Overall rate	2/44 (5%)	1/39 (3%)	2/40 (5%)
Adjusted rate	6.9%	3.6%	8.7%
Terminal rate	2/29 (7%)	1/28 (4%)	2/23 (9%)
First incidence (days)	734 (T)	734 (T)	734 (T)
Life table test	P=0.509	P=0.512N	P=0.610
Logistic regression test	P=0.509	P=0.512N	P=0.610
Cochran-Armitage test	P=0.567		
Fisher exact test		P=0.546N	P=0.655

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
Clitoral Gland: Adenoma or Carcinoma			
Overall rate	7/44 (16%)	1/39 (3%)	4/40 (10%)
Adjusted rate	21.7%	3.6%	17.4%
Terminal rate	5/29 (17%)	1/28 (4%)	4/23 (17%)
First incidence (days)	650	734 (T)	734 (T)
Life table test	P=0.452N	P=0.040N	P=0.415N
Logistic regression test	P=0.446N	P=0.042N	P=0.409N
Cochran-Armitage test	P=0.357N		
Fisher exact test		P=0.042N	P=0.318N
Mammary Gland: Carcinoma			
Overall rate	5/51 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate	15.1%	9.0%	13.0%
Terminal rate	4/30 (13%)	1/28 (4%)	3/23 (13%)
First incidence (days)	465	645	734 (T)
Life table test	P=0.469N	P=0.397N	P=0.492N
Logistic regression test	P=0.393N	P=0.368N	P=0.427N
Cochran-Armitage test	P=0.347N		
Fisher exact test		P=0.369N	P=0.369N
Mammary Gland: Adenoma or Carcinoma			
Overall rate	6/51 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	17.8%	9.0%	13.0%
Terminal rate	4/30 (13%)	1/28 (4%)	3/23 (13%)
First incidence (days)	465	645	734 (T)
Life table test	P=0.359N	P=0.285N	P=0.377N
Logistic regression test	P=0.288N	P=0.255N	P=0.314N
Cochran-Armitage test	P=0.243N		
Fisher exact test		P=0.254N	P=0.254N
Mammary Gland: Fibroadenoma			
Overall rate	21/51 (41%)	12/50 (24%)	7/50 (14%)
Adjusted rate	58.6%	36.8%	24.4%
Terminal rate	16/30 (53%)	8/28 (29%)	4/23 (17%)
First incidence (days)	331	650	585
Life table test	P=0.016N	P=0.079N	P=0.015N
Logistic regression test	P=0.005N	P=0.057N	P=0.004N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.051N	P=0.002N
Mammary Gland: Fibroma, Fibroadenoma, or Adenoma			
Overall rate	22/51 (43%)	12/50 (24%)	8/50 (16%)
Adjusted rate	59.9%	36.8%	26.2%
Terminal rate	16/30 (53%)	8/28 (29%)	4/23 (17%)
First incidence (days)	331	650	549
Life table test	P=0.023N	P=0.058N	P=0.022N
Logistic regression test	P=0.006N	P=0.038N	P=0.004N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.034N	P=0.003N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
Mammary Gland: Fibroma, Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	25/51 (49%)	14/50 (28%)	11/50 (22%)
Adjusted rate	66.3%	41.6%	37.8%
Terminal rate	18/30 (60%)	9/28 (32%)	7/23 (30%)
First incidence (days)	331	645	549
Life table test	P=0.043N	P=0.047N	P=0.035N
Logistic regression test	P=0.010N	P=0.027N	P=0.007N
Cochran-Armitage test	P=0.006N		
Fisher exact test		P=0.024N	P=0.004N
Pancreatic Islets: Adenoma			
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	9.2%	3.6%	13.0%
Terminal rate	2/30 (7%)	1/28 (4%)	3/23 (13%)
First incidence (days)	679	734 (T)	734 (T)
Life table test	P=0.422	P=0.341N	P=0.534
Logistic regression test	P=0.427	P=0.333N	P=0.544
Cochran-Armitage test	P=0.541		
Fisher exact test		P=0.309N	P=0.661N
Pancreatic Islets: Carcinoma			
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.7%	10.7%	0.0%
Terminal rate	2/30 (7%)	3/28 (11%)	0/23 (0%)
First incidence (days)	734 (T)	734 (T)	–
Life table test	P=0.226N	P=0.468	P=0.298N
Logistic regression test	P=0.226N	P=0.468	P=0.298N
Cochran-Armitage test	P=0.165N		
Fisher exact test		P=0.500	P=0.247N
Pancreatic Islets: Adenoma or Carcinoma			
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted rate	15.7%	14.3%	13.0%
Terminal rate	4/30 (13%)	4/28 (14%)	3/23 (13%)
First incidence (days)	679	734 (T)	734 (T)
Life table test	P=0.463N	P=0.551N	P=0.509N
Logistic regression test	P=0.469N	P=0.566N	P=0.508N
Cochran-Armitage test	P=0.315N		
Fisher exact test		P=0.500N	P=0.357N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	38/50 (76%)	33/49 (67%)	33/48 (69%)
Adjusted rate	87.9%	76.0%	93.8%
Terminal rate	25/30 (83%)	18/28 (64%)	21/23 (91%)
First incidence (days)	458	434	430
Life table test	P=0.316	P=0.400N	P=0.360
Logistic regression test	P=0.417N	P=0.240N	P=0.443N
Cochran-Armitage test	P=0.303N		
Fisher exact test		P=0.232N	P=0.282N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	40/50 (80%)	35/49 (71%)	34/48 (71%)
Adjusted rate	88.6%	78.9%	94.0%
Terminal rate	25/30 (83%)	19/28 (68%)	21/23 (91%)
First incidence (days)	458	434	430
Life table test	P=0.363	P=0.413N	P=0.403
Logistic regression test	P=0.332N	P=0.231N	P=0.370N
Cochran-Armitage test	P=0.220N		
Fisher exact test		P=0.224N	P=0.206N
Thyroid Gland (C-cell): Carcinoma			
Overall rate	6/50 (12%)	5/50 (10%)	2/50 (4%)
Adjusted rate	18.9%	14.8%	7.6%
Terminal rate	5/30 (17%)	3/28 (11%)	1/23 (4%)
First incidence (days)	656	494	675
Life table test	P=0.186N	P=0.543N	P=0.231N
Logistic regression test	P=0.132N	P=0.514N	P=0.204N
Cochran-Armitage test	P=0.107N		
Fisher exact test		P=0.500N	P=0.134N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	6/50 (12%)	5/50 (10%)	3/50 (6%)
Adjusted rate	18.9%	14.8%	11.8%
Terminal rate	5/30 (17%)	3/28 (11%)	2/23 (9%)
First incidence (days)	656	494	675
Life table test	P=0.325N	P=0.543N	P=0.382N
Logistic regression test	P=0.252N	P=0.514N	P=0.354N
Cochran-Armitage test	P=0.205N		
Fisher exact test		P=0.500N	P=0.243N
Thyroid Gland (Follicular Cell): Carcinoma			
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.3%	3.6%	2.4%
Terminal rate	1/30 (3%)	1/28 (4%)	0/23 (0%)
First incidence (days)	465	734 (T)	569
Life table test	P=0.320N	P=0.326N	P=0.352N
Logistic regression test	P=0.187N	P=0.260N	P=0.165N
Cochran-Armitage test	P=0.272N		
Fisher exact test		P=0.309N	P=0.309N
Uterus: Stromal Polyp			
Overall rate	2/51 (4%)	3/50 (6%)	6/50 (12%)
Adjusted rate	6.7%	10.7%	22.0%
Terminal rate	2/30 (7%)	3/28 (11%)	4/23 (17%)
First incidence (days)	734 (T)	734 (T)	367
Life table test	P=0.042	P=0.468	P=0.073
Logistic regression test	P=0.065	P=0.468	P=0.114
Cochran-Armitage test	P=0.086		
Fisher exact test		P=0.491	P=0.128

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rate	2/51 (4%)	3/50 (6%)	7/50 (14%)
Adjusted rate	6.7%	10.7%	23.7%
Terminal rate	2/30 (7%)	3/28 (11%)	4/23 (17%)
First incidence (days)	734 (T)	734 (T)	367
Life table test	P=0.020	P=0.468	P=0.043
Logistic regression test	P=0.037	P=0.468	P=0.078
Cochran-Armitage test	P=0.043		
Fisher exact test		P=0.491	P=0.075
All Organs: Leukemia (Monocytic or Mononuclear Cell)			
Overall rate	17/51 (33%)	15/50 (30%)	16/50 (32%)
Adjusted rate	39.4%	38.1%	44.8%
Terminal rate	6/30 (20%)	6/28 (21%)	5/23 (22%)
First incidence (days)	458	545	344
Life table test	P=0.351	P=0.510N	P=0.398
Logistic regression test	P=0.447N	P=0.425N	P=0.448N
Cochran-Armitage test	P=0.524N		
Fisher exact test		P=0.442N	P=0.528N
All Organs: Benign Neoplasms			
Overall rate	47/51 (92%)	41/50 (82%)	40/50 (80%)
Adjusted rate	97.9%	90.9%	94.9%
Terminal rate	29/30 (97%)	24/28 (86%)	21/23 (91%)
First incidence (days)	331	434	367
Life table test	P=0.340	P=0.381N	P=0.404
Logistic regression test	P=0.129N	P=0.112N	P=0.098N
Cochran-Armitage test	P=0.086N		
Fisher exact test		P=0.110N	P=0.069N
All Organs: Malignant Neoplasms			
Overall rate	32/51 (63%)	27/50 (54%)	24/50 (48%)
Adjusted rate	70.3%	64.1%	61.2%
Terminal rate	17/30 (57%)	14/28 (50%)	9/23 (39%)
First incidence (days)	458	494	344
Life table test	P=0.429N	P=0.377N	P=0.435N
Logistic regression test	P=0.076N	P=0.235N	P=0.081N
Cochran-Armitage test	P=0.096N		
Fisher exact test		P=0.245N	P=0.098N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
All Organs: Benign or Malignant Neoplasms			
Overall rate	51/51 (100%)	48/50 (96%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	95.9%
Terminal rate	30/30 (100%)	28/28 (100%)	21/23 (91%)
First incidence (days)	331	434	344
Life table test	P=0.173	P=0.539	P=0.215
Logistic regression test	P=0.124N	P=0.218N	P=0.104N
Cochran-Armitage test	P=0.109N		
Fisher exact test		P=0.243N	P=0.118N

(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, mammary gland, pancreatic islets, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the 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 controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Pituitary Gland (Pars Distalis) Adenomas in Untreated Female F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence: Dermal (Acetone)	
Total	19/47 (40.4%)
Overall Historical Incidence: Feed	
Total	725/1,345 (53.9%)
Standard deviation	11.3%
Range	30%-74%
Overall Historical Incidence: Inhalation	
Total	229/395 (58.0%)
Standard deviation	3.4%
Range	53%-62%
Overall Historical Incidence: Water Gavage	
Total	170/365 (46.6%)
Standard deviation	6.7%
Range	39%-58%
Overall Historical Incidence: Corn Oil Gavage	
Total	513/1,054 (48.7%)
Standard deviation	9.8%
Range	27%-63%

[a] Data as of 31 March 1993

TABLE B4b
Historical Incidence of Mammary Gland Fibroadenomas in Untreated Female F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence: Dermal (Acetone)	
Total	20/50 (40.0%)
Overall Historical Incidence: Feed	
Total	521/1,351 (38.6%)
Standard deviation	13.1%
Range	8%-58%
Overall Historical Incidence: Inhalation	
Total	98/400 (24.5%)
Standard deviation	5.5%
Range	16%-32%
Overall Historical Incidence: Water Gavage	
Total	143/368 (38.9%)
Standard deviation	13.6%
Range	16%-53%
Overall Historical Incidence: Corn Oil Gavage	
Total	387/1,070 (36.2%)
Standard deviation	10.2%
Range	18%-56%

[a] Data as of 31 March 1993

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

	0 μL	100 μL	300 μL
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	9	10	10
Early deaths			
Moribund	12	12	17
Natural deaths	9	10	10
Survivors			
Died last week of study			2
Terminal sacrifice	30	28	21
Animals examined microscopically	60	52	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(9)	(2)	(10)
Hepatodiaphragmatic nodule	1 (11%)		
Inflammation, granulomatous, focal	5 (56%)	1 (50%)	2 (20%)
Necrosis, focal		1 (50%)	
Bile duct, hyperplasia	6 (67%)	1 (50%)	7 (70%)
Pancreas	(9)		(10)
Acinus, atrophy	1 (11%)		2 (20%)
Cardiovascular System			
Heart	(9)	(1)	(10)
Cardiomyopathy	4 (44%)	1 (100%)	7 (70%)
Endocrine System			
Adrenal gland, cortex	(9)		(10)
Hyperplasia, focal	3 (33%)		
Pituitary gland	(9)	(1)	(10)
Pars distalis, cyst	1 (11%)		
Pars distalis, hyperplasia, focal	3 (33%)	1 (100%)	1 (10%)
Hematopoietic System			
Spleen	(9)	(2)	(10)
Necrosis, focal		1 (50%)	
Pigmentation, hemosiderin	8 (89%)	2 (100%)	10 (100%)
Thymus	(9)		(10)
Cyst	1 (11%)		
Integumentary System			
Mammary gland	(9)	(1)	(10)
Hyperplasia, cystic	7 (78%)	1 (100%)	5 (50%)

[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 Diethylphthalate (continued)

	0 μL	100 μL	300 μL
15-Month Interim Evaluation (continued)			
Nervous System			
Brain	(9)		(10)
Cerebrum, compression	1 (11%)		
Respiratory System			
Lung	(9)		(10)
Atelectasis, focal	1 (11%)		
Alveolus, infiltration cellular, histiocyte	1 (11%)		
Nose	(9)	(1)	(10)
Exudate			1 (10%)
Foreign body			2 (20%)
Inflammation, suppurative		1 (100%)	
Nasolacrimal duct, exudate	2 (22%)		
Special Senses System			
Eye	(1)		
Cataract	1 (100%)		
Retina, atrophy	1 (100%)		
Retrobulbar, hemorrhage	1 (100%)		
Urinary System			
Kidney	(9)	(1)	(10)
Nephropathy	5 (56%)	1 (100%)	8 (80%)
Cortex, mineralization, focal	3 (33%)		2 (20%)
Pelvis, epithelium, hyperplasia	3 (33%)		5 (50%)
Pelvis, epithelium, mineralization, focal	3 (33%)		4 (40%)
Systems Examined With No Lesions Observed			
General Body System			
Genital System			
Musculoskeletal System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(49)	(50)
Hyperkeratosis	1 (2%)	3 (6%)	
Intestine large, cecum	(48)	(45)	(46)
Ulcer			1 (2%)
Intestine large, colon	(49)	(47)	(48)
Edema		2 (4%)	2 (4%)
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)
Intestine small, duodenum	(49)	(49)	(48)
Ulcer			1 (2%)
Mucosa, erosion, focal		1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Alimentary System (continued)			
Intestine small, ileum	(46)	(44)	(43)
Mucosa, atrophy	1 (2%)		
Intestine small, jejunum	(46)	(46)	(46)
Mucosa, atrophy	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	4 (8%)	1 (2%)
Basophilic focus	16 (32%)	11 (22%)	6 (12%)
Clear cell focus	2 (4%)	3 (6%)	3 (6%)
Congestion		1 (2%)	
Degeneration, fatty	23 (46%)	11 (22%)	3 (6%)
Eosinophilic focus		1 (2%)	
Hematopoietic cell proliferation			1 (2%)
Hepatodiaphragmatic nodule	7 (14%)	10 (20%)	3 (6%)
Infiltration cellular, histiocyte, focal			1 (2%)
Inflammation, chronic, focal	25 (50%)	24 (48%)	27 (54%)
Mitotic alteration		1 (2%)	
Mixed cell focus	1 (2%)		2 (4%)
Necrosis	2 (4%)	3 (6%)	2 (4%)
Pigmentation, focal			1 (2%)
Bile duct, hyperplasia	27 (54%)	27 (54%)	28 (56%)
Hepatocyte, hyperplasia			1 (2%)
Periportal, infiltration cellular, mixed cell		1 (2%)	
Subserosa, angiectasis		1 (2%)	
Mesentery	(3)	(3)	(1)
Hemorrhage		1 (33%)	
Polyarteritis			1 (100%)
Fat, granuloma	2 (67%)	1 (33%)	
Pancreas	(50)	(50)	(50)
Cytoplasmic alteration, focal		1 (2%)	2 (4%)
Edema		1 (2%)	
Fibrosis	1 (2%)		
Fibrosis, focal			1 (2%)
Inflammation, focal			1 (2%)
Acinus, atrophy	9 (18%)	16 (32%)	14 (28%)
Stomach, forestomach	(50)	(50)	(50)
Acanthosis	16 (32%)	13 (26%)	11 (22%)
Cyst epithelial inclusion			1 (2%)
Edema	6 (12%)	4 (8%)	6 (12%)
Hemorrhage	2 (4%)		1 (2%)
Hyperkeratosis	14 (28%)	11 (22%)	8 (16%)
Ulcer	7 (14%)	4 (8%)	4 (8%)
Serosa, inflammation, proliferative	1 (2%)		
Stomach, glandular	(50)	(50)	(50)
Ulcer		1 (2%)	2 (4%)
Mucosa, erosion, focal	1 (2%)	1 (2%)	2 (4%)
Tooth			(1)
Inflammation, suppurative			1 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Cardiovascular System			
Blood vessel		(2)	
Polyarteritis		1 (50%)	
Heart	(50)	(50)	(50)
Abscess			1 (2%)
Cardiomyopathy	43 (86%)	33 (66%)	31 (62%)
Atrium, thrombus		2 (4%)	3 (6%)
Myocardium, mineralization, focal			1 (2%)
Endocrine System			
Adrenal gland, cortex	(51)	(50)	(50)
Angiectasis	1 (2%)		
Degeneration, fatty, focal	15 (29%)	8 (16%)	9 (18%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia, focal	10 (20%)	12 (24%)	8 (16%)
Hypertrophy, focal			1 (2%)
Thrombus		1 (2%)	
Adrenal gland, medulla	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)	3 (6%)	5 (10%)
Islets, pancreatic	(50)	(50)	(50)
Cytomegaly		1 (2%)	
Hyperplasia	2 (4%)		
Parathyroid gland	(45)	(50)	(47)
Hypertrophy	7 (16%)	4 (8%)	2 (4%)
Pituitary gland	(50)	(49)	(48)
Angiectasis	4 (8%)	6 (12%)	3 (6%)
Hemorrhage	1 (2%)		1 (2%)
Pars distalis, hyperplasia, focal	4 (8%)	6 (12%)	8 (17%)
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	
C-cell, hyperplasia	8 (16%)	6 (12%)	6 (12%)
Follicle, dilatation		3 (6%)	4 (8%)
Follicular cell, hyperplasia			2 (4%)
General Body System			
Tissue NOS	(2)	(2)	(2)
Abscess	1 (50%)		1 (50%)
Genital System			
Clitoral gland	(44)	(39)	(40)
Cyst		1 (3%)	
Ectasia	6 (14%)	2 (5%)	5 (13%)
Fibrosis	3 (7%)	1 (3%)	3 (8%)
Granuloma	1 (2%)		
Hyperplasia		1 (3%)	
Inflammation, chronic	1 (2%)	2 (5%)	
Inflammation, suppurative	3 (7%)	2 (5%)	1 (3%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	100 µL	300 µL
2-Year Study (continued)			
Genital System (continued)			
Ovary	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	2 (4%)
Cyst	1 (2%)	1 (2%)	4 (8%)
Uterus	(50)	(50)	(50)
Dilatation	1 (2%)	2 (4%)	1 (2%)
Inflammation			1 (2%)
Endometrium, atrophy	23 (46%)	24 (48%)	15 (30%)
Vagina	(1)		(1)
Exudate			1 (100%)
Hematopoietic System			
Bone marrow	(48)	(49)	(49)
Hypoplasia	1 (2%)	1 (2%)	1 (2%)
Lymph node, mandibular	(50)	(50)	(50)
Hyperplasia	1 (2%)		
Spleen	(51)	(50)	(50)
Congestion		1 (2%)	
Fibrosis			2 (4%)
Hematocyst	1 (2%)		
Hematopoietic cell proliferation	30 (59%)	26 (52%)	22 (44%)
Hyperplasia, lymphoid	1 (2%)		
Infarct		1 (2%)	
Pigmentation, hemosiderin	16 (31%)	19 (38%)	17 (34%)
Capsule, hyperplasia			1 (2%)
Thymus	(44)	(43)	(42)
Congestion		1 (2%)	
Cyst	1 (2%)	1 (2%)	1 (2%)
Depletion lymphoid	2 (5%)	2 (5%)	1 (2%)
Integumentary System			
Mammary gland	(50)	(48)	(50)
Hyperplasia	9 (18%)	9 (19%)	9 (18%)
Lactation	44 (88%)	42 (88%)	43 (86%)
Skin	(50)	(49)	(50)
Other, acanthosis	2 (4%)		1 (2%)
Other, hyperkeratosis			1 (2%)
Other, inflammation, chronic		1 (2%)	
Skin, control	(50)	(49)	(50)
Acanthosis	3 (6%)		
Skin, site of application-no mass	(50)	(49)	(50)
Acanthosis	8 (16%)	18 (37%)	23 (46%)
Inflammation, chronic			1 (2%)
Ulcer	1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Musculoskeletal System			
Bone	(48)	(49)	(50)
Fibrous osteodystrophy	1 (2%)		1 (2%)
Hyperostosis	1 (2%)		1 (2%)
Osteopetrosis		2 (4%)	
Nervous System			
Brain	(50)	(50)	(50)
Compression	7 (14%)	5 (10%)	9 (18%)
Hemorrhage, focal		1 (2%)	
Hydrocephalus		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Atelectasis			1 (2%)
Congestion	18 (36%)	15 (30%)	14 (28%)
Hemorrhage	1 (2%)	1 (2%)	
Infiltration cellular, histiocyte	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic	8 (16%)	7 (14%)	4 (8%)
Alveolar epithelium, hyperplasia	1 (2%)		1 (2%)
Nose	(51)	(49)	(50)
Foreign body		1 (2%)	2 (4%)
Fungus	3 (6%)		1 (2%)
Inflammation, chronic	10 (20%)	18 (37%)	16 (32%)
Inflammation, suppurative	3 (6%)	1 (2%)	2 (4%)
Nares, ulcer	1 (2%)		
Nasolacrimal duct, inflammation, suppurative		4 (8%)	2 (4%)
Trachea	(50)	(50)	(50)
Glands, dilatation			1 (2%)
Special Senses System			
Eye	(46)	(44)	(39)
Cataract	46 (100%)	44 (100%)	39 (100%)
Hemorrhage	5 (11%)		2 (5%)
Inflammation	1 (2%)		
Inflammation, chronic		1 (2%)	
Phthisis bulbi		1 (2%)	
Cornea, hyperplasia, squamous, focal		1 (2%)	
Cornea, inflammation	2 (4%)	4 (9%)	3 (8%)
Retina, atrophy	40 (87%)	38 (86%)	32 (82%)
Zymbal's gland	(1)	(1)	(1)
Abscess		1 (100%)	
Cyst	1 (100%)		1 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	100 μL	300 μL
2-Year Study (continued)			
Urinary System			
Kidney	(51)	(50)	(50)
Hydronephrosis	1 (2%)		
Inflammation, suppurative		1 (2%)	2 (4%)
Nephropathy	47 (92%)	45 (90%)	47 (94%)
Collecting tubule, casts		1 (2%)	
Medulla, necrosis			1 (2%)
Pelvis, dilatation	3 (6%)	3 (6%)	
Pelvis, epithelium, hyperplasia	19 (37%)	23 (46%)	21 (42%)
Pelvis, epithelium, mineralization	14 (27%)	16 (32%)	13 (26%)
Perirenal tissue, inflammation, suppurative	1 (2%)	1 (2%)	
Proximal convoluted renal tubule, necrosis	1 (2%)	1 (2%)	2 (4%)
Proximal convoluted renal tubule, pigmentation	1 (2%)	2 (4%)	
Renal tubule, mineralization	2 (4%)	2 (4%)	2 (4%)
Renal tubule, necrosis		1 (2%)	
Urinary bladder	(48)	(47)	(49)
Inflammation, chronic	1 (2%)		
Lumen, hemorrhage		1 (2%)	

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

TABLE C1	Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate	148
TABLE C2	Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate	152
TABLE C3	Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate	174
TABLE C4	Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice	178
TABLE C5	Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate	179

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

	0 μL	7.5 μL	15 μL	30 μL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		
Moribund	2	3	2	1
Natural deaths	5	4	2	6
Survivors				
Terminal sacrifice	43	41	46	43
Missing		1		
Animals examined microscopically	60	53	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)	(1)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma	1 (10%)	2 (67%)		1 (10%)
Hepatocellular adenoma, multiple			1 (100%)	1 (10%)
Respiratory System				
Lung	(10)			(10)
Alveolar/bronchiolar adenoma	1 (10%)			1 (10%)
Special Senses System				
Harderian gland	(1)			
Adenoma	1 (100%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine small, duodenum	(47)	(49)	(48)	(46)
Intestine small, jejunum	(47)	(49)	(48)	(46)
Intestine small, ileum	(47)	(48)	(48)	(46)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Adenoma, multiple	1 (2%)			
Hemangiosarcoma		1 (2%)		1 (2%)
Hemangiosarcoma, multiple	1 (2%)			1 (2%)
Hepatocellular carcinoma	3 (6%)	3 (6%)	5 (10%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hepatocellular adenoma	5 (10%)	9 (18%)	7 (14%)	9 (18%)
Hepatocellular adenoma, multiple	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Histiocytic sarcoma		1 (2%)		
Mesentery	(2)	(2)	(2)	
Hemangioma		1 (50%)		
Pancreas	(50)	(49)	(50)	(50)
Acinus, carcinoma				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Adenoma	6 (12%)	3 (6%)	2 (4%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Capsule, adenoma	3 (6%)	2 (4%)		2 (4%)
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma benign			1 (2%)	
Pituitary gland	(48)	(47)	(48)	(49)
Histiocytic sarcoma, metastatic		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	2 (4%)	1 (2%)	3 (6%)	
General Body System				
Tissue NOS	(3)	(1)	(2)	(1)
Hemangioma				1 (100%)
Lipoma	1 (33%)		1 (50%)	
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Sarcoma	1 (2%)			
Penis	(1)	(1)		
Prostate	(50)	(49)	(50)	(50)
Testes	(50)	(49)	(50)	(50)
Interstitial cell, adenoma		1 (2%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
2-Year Study (continued)				
Hematopoietic System				
Lymph node	(2)	(1)		(1)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (50%)			
Lymph node, mandibular	(44)	(47)	(47)	(49)
Lymph node, mesenteric	(47)	(50)	(47)	(50)
Hemangiosarcoma			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	4 (8%)		5 (10%)	1 (2%)
Hemangiosarcoma, multiple	2 (4%)			1 (2%)
Thymus	(29)	(39)	(37)	(32)
Hemangiosarcoma	1 (3%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, paraganglioma benign	1 (2%)			
Musculoskeletal System				
Bone	(50)	(48)	(50)	(50)
Vertebra, osteosarcoma			1 (2%)	
Skeletal muscle		(1)	(1)	(1)
Diaphragm, carcinoma, metastatic, pancreas				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	1 (2%)	6 (12%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	5 (10%)	5 (10%)	4 (8%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Carcinoma, metastatic, liver				1 (2%)
Carcinoma, metastatic, pancreas				1 (2%)
Hemangiosarcoma	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Nose	(50)	(49)	(50)	(50)
Special Senses System				
Harderian gland		(2)	(3)	
Adenoma		2 (100%)	3 (100%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)		1 (2%)
Lymphoma malignant mixed	2 (4%)	2 (4%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	2	1	3
2-Year study	27	26	33	29
Total primary neoplasms				
15-Month interim evaluation	3	2	1	4
2-Year study	49	38	44	41
Total animals with benign neoplasms				
15-Month interim evaluation	3	2	1	3
2-Year study	16	18	23	20
Total benign neoplasms				
15-Month interim evaluation	3	2	1	3
2-Year study	25	23	27	23
Total animals with malignant neoplasms				
2-Year study	19	14	15	16
Total malignant neoplasms				
2-Year study	24	15	17	18
Total animals with metastatic neoplasms				
2-Year study	2	3	2	5
Total metastatic neoplasms				
2-Year study	2	5	2	8

[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 Diethylphthalate: 0 μL

Number of Days on Study	4 3 1	5 3 6	5 5 8	6 2 0	6 3 5	6 9 0	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 4 2 1	0 1 1 1	0 5 2 1	0 3 0 1	0 1 3 1	0 4 9 1	0 4 8 1	0 1 2 1	0 1 4 1	0 1 5 1	0 1 6 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 5 1 1	0 5 3 1	0 5 4 1	0 5 5 1	0 2 1 1	0 2 2 1	0 2 3 1	0 2 4 1	0 2 5 1	0 5 6 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple														X											
Hemangiosarcoma, multiple			X																						
Hepatocellular carcinoma					X																		X		
Hepatocellular carcinoma, multiple														X											
Hepatocellular adenoma									X																X
Hepatocellular adenoma, multiple														X											
Mesentery				+		+																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X								X					
Capsule, adenoma																								X	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X												X										
General Body System																									
Tissue NOS						+						+					+								
Lipoma												X													
Genital System																									
Coagulating gland							+																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma												X													
Penis																									

+: 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 Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 5 7 1	0 5 8 1	0 5 9 1	0 6 0 1	0 2 6 1	0 2 7 1	0 2 8 1	0 2 9 1	0 4 1 1	0 4 3 1	0 4 4 1	0 4 5 1	0 3 1 1	0 3 2 1	0 3 3 1	0 3 4 1	0 3 5 1	0 4 6 1	0 4 7 1	0 5 0 1	0 3 6 1	0 3 7 1	0 3 8 1	0 3 9 1	0 4 0 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, multiple																									1
Hemangiosarcoma, multiple																									1
Hepatocellular carcinoma							X																		3
Hepatocellular carcinoma, multiple																									1
Hepatocellular adenoma			X						X												X				5
Hepatocellular adenoma, multiple																									1
Mesentery																									2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X	X						X						X				6
Capsule, adenoma									X														X		3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																									2
General Body System																									
Tissue NOS																									3
Lipoma																									1
Genital System																									
Coagulating gland																									1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																									1
Penis			+																						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	4 3 1	5 3 6	5 5 8	6 2 0	6 3 5	6 9 0	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 4 2 1	0 1 1 1	0 5 2 1	0 3 0 1	0 1 3 1	0 4 9 1	0 4 8 1	0 1 2 1	0 1 4 1	0 1 5 1	0 1 6 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 5 1 1	0 5 3 1	0 5 4 1	0 5 5 1	0 2 1 1	0 2 2 1	0 2 3 1	0 2 4 1	0 2 5 1	0 5 6 1
Genital System (continued)																									
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung									X																
Lymph node, mandibular	+	I	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Lymph node, mesenteric	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Hemangiosarcoma, multiple															X									X	
Thymus	+	M	+	+	+	M	+	M	M	+	+	M	M	M	M	+	M	+	M	+	+	+	+	+	M
Hemangiosarcoma																									
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Subcutaneous tissue, hemangiosarcoma																					X				
Subcutaneous tissue, paraganglioma benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X			X			X									X	
Alveolar/bronchiolar carcinoma									X			X								X					
Hemangiosarcoma																							X		
Hepatocellular carcinoma, metastatic, liver														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	0 5 7 1	0 5 8 1	0 5 9 1	0 6 0 1	0 2 6 1	0 2 7 1	0 2 8 1	0 2 9 1	0 4 1 1	0 4 3 1	0 4 4 1	0 4 5 1	0 3 1 1	0 3 2 1	0 3 3 1	0 3 4 1	0 3 5 1	0 4 6 1	0 4 7 1	0 5 0 1	0 3 6 1	0 3 7 1	0 3 8 1	0 3 9 1	0 4 0 1	Total Tissues/ Tumors
Genital System (continued)																									
Preputial gland																		+							1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+																						2
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X			X																X				4
Hemangiosarcoma, multiple																									2
Thymus	M	+	M	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	M	M	M	29
Hemangiosarcoma																	X								1
Integumentary System																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Subcutaneous tissue, hemangiosarcoma																									1
Subcutaneous tissue, paraganglioma benign															X										1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																			5
Alveolar/bronchiolar carcinoma	X				X																				5
Hemangiosarcoma																									1
Hepatocellular carcinoma, metastatic, liver																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	5	2	3	9	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	6	8	0	5	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
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	0
	4	1	5	3	1	4	4	1	1	1	1	1	1	1	2	5	5	5	5	2	2	2	2	2	5	
	2	1	2	0	3	9	8	2	4	5	6	7	8	9	0	1	3	4	5	1	2	3	4	5	6	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL

Number of Days on Study	0 2 9	1 6 5	3 7 8	3 9 7	5 7 6	5 9 0	5 9 0	6 8 0	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 6 3 1	1 7 3 1	1 3 6 1	1 4 3 1	1 4 0 1	1 4 1 1	1 7 9 1	1 3 1 1	1 7 7 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 0 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1	1 5 5 1	1 4 6 1	1 4 7 1	1 4 8 1	1 4 9 1	1 5 0 1	1 6 1 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small; jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma					X				X							X									
Hepatocellular carcinoma, multiple						X																			
Hepatocellular adenoma					X					X	X				X						X				
Hepatocellular adenoma, multiple												X													
Histiocytic sarcoma			X																						
Mesentery																							+		
Hemangioma																							X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Hepatocellular carcinoma, metastatic, liver									X																
Capsule, adenoma																								X	
Adrenal gland								+																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma, metastatic			X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS															+										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 6 2 1	1 6 4 1	1 6 5 1	1 7 1 1	1 7 2 1	1 7 4 1	1 7 5 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 5 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 2 1	1 4 4 1	1 4 5 1	1 6 6 1	1 6 7 1	1 6 8 1	1 6 9 1	1 7 0 1	1 7 6 1	1 7 8 1	1 8 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Hepatocellular carcinoma																										3
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X							X								X				X			9
Hepatocellular adenoma, multiple												X														2
Histiocytic sarcoma																										1
Mesentery					+																					2
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X																	X					3
Hepatocellular carcinoma, metastatic, liver																										1
Capsule, adenoma	X																									2
Adrenal gland													+													2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma, metastatic																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X																									1
General Body System																										
Tissue NOS																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	0 2 9	1 6 5	3 7 8	3 9 7	5 7 6	5 9 0	5 9 0	6 8 0	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 6 3 1	1 7 3 1	1 3 6 1	1 4 3 1	1 4 0 1	1 4 1 1	1 7 9 1	1 3 1 1	1 7 7 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 0 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1	1 5 5 1	1 4 6 1	1 4 7 1	1 4 8 1	1 4 9 1	1 5 0 1	1 6 1 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis				+																					
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																							X		
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar adenoma, multiple											X														
Alveolar/bronchiolar carcinoma																					X				X
Alveolar/bronchiolar carcinoma, multiple																		X							
Hepatocellular carcinoma, metastatic, liver					X				X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+																				
Harderian gland					+	+																			
Adenoma					X	X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 6 2 1	1 6 4 1	1 6 5 1	1 7 1 1	1 7 2 1	1 7 4 1	1 7 5 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 5 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 2 1	1 4 4 1	1 4 5 1	1 6 6 1	1 6 7 1	1 6 8 1	1 6 9 1	1 7 0 1	1 7 6 1	1 7 8 1	1 8 0 1	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																									1
Preputial gland																	+								1
Prostate	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+		+	+	+	M	+	+	+	I	+	M	M	+	+	+	M	+	M	39
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M		M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									1
Alveolar/bronchiolar adenoma, multiple																									1
Alveolar/bronchiolar carcinoma					X					X									X						5
Alveolar/bronchiolar carcinoma, multiple																									1
Hepatocellular carcinoma, metastatic, liver																									2
Nose	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye																									1
Harderian gland																									2
Adenoma																									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 6 2 1	1 6 4 1	1 6 5 1	1 7 1 1	1 7 2 1	1 7 4 1	1 7 5 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 5 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 2 1	1 4 4 1	1 4 5 1	1 6 6 1	1 6 7 1	1 6 8 1	1 6 9 1	1 7 0 1	1 7 6 1	1 7 8 1	1 8 0 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed				X																						2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 9 8 1	2 9 9 1	3 0 0 1	2 7 1 1	2 7 2 1	2 7 3 1	2 7 5 1	2 8 1 1	2 8 2 1	2 8 3 1	2 8 4 1	2 8 5 1	2 7 7 1	2 7 8 1	2 7 9 1	2 8 0 1	2 5 1 1	2 5 2 1	2 5 3 1	2 5 4 1	2 5 5 1	2 6 1 1	2 6 2 1	2 6 4 1	2 6 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma											X															5
Hepatocellular carcinoma, multiple			X																							1
Hepatocellular adenoma		X	X										X				X							X		7
Hepatocellular adenoma, multiple					X															X						2
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Adrenal gland																		+								2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X							X							3
General Body System																										
Tissue NOS																										2
Lipoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma							X																			1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 9 8 1	2 9 9 1	3 0 0 1	2 7 1 1	2 7 2 1	2 7 3 1	2 7 5 1	2 8 1 1	2 8 2 1	2 8 3 1	2 8 4 1	2 8 5 1	2 7 7 1	2 7 8 1	2 7 9 1	2 8 0 1	2 5 1 1	2 5 2 1	2 5 3 1	2 5 4 1	2 5 5 1	2 6 1 1	2 6 2 1	2 6 4 1	2 6 5 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	47
Hemangiosarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				5
Thymus	I	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	37
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																					X					1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																		X						6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma														X		X		X								4
Hepatocellular carcinoma, metastatic, liver											X															2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Harderian gland	+																	+								3
Adenoma	X																	X								3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL

Number of Days on Study	5 1 2	5 5 6	5 7 7	6 4 4	6 7 5	6 9 8	7 0 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 8 7 1	3 7 1 1	3 8 2 1	3 9 6 1	4 0 8 1	3 7 5 1	4 0 2 1	4 0 6 1	4 0 7 1	4 0 9 1	4 0 0 1	4 1 1 1	3 8 3 1	3 8 4 1	3 8 4 1	3 8 5 1	3 9 1 1	3 9 2 1	3 9 3 1	3 9 4 1	3 9 5 1	3 8 6 1	3 8 8 1	3 8 9 1	3 9 0 1	4 0 1 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hemangiosarcoma, multiple														X											
Hepatocellular carcinoma		X	X		X																		X		
Hepatocellular carcinoma, multiple				X																					
Hepatocellular adenoma											X	X		X											X
Hepatocellular adenoma, multiple																		X					X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, carcinoma				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															X
Capsule, adenoma																									
Adrenal gland																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																				+					
Hemangioma																				X					
Genital System																									
Coagulating gland					+																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	4 0 3 1	4 0 4 1	4 0 5 1	3 7 2 1	3 7 3 1	3 7 4 1	3 7 6 1	3 7 7 1	3 7 8 1	3 7 9 1	3 7 0 1	4 8 1 1	4 1 2 1	4 1 3 1	4 1 4 1	4 1 5 1	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 1 6 1	4 1 7 1	4 1 8 1	4 1 9 1	4 2 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma																										4
Hepatocellular carcinoma, multiple							X											X								3
Hepatocellular adenoma									X					X						X	X				X	9
Hepatocellular adenoma, multiple																			X							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+			+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+			+	48
Tooth					+																					1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Capsule, adenoma	X		X																							2
Adrenal gland											+															1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																										1
Hemangioma																										1
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	5 1 2	5 5 6	5 7 7	6 4 4	6 7 5	6 9 8	7 0 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 8 7 1	3 7 1 1	3 8 2 1	3 9 6 1	4 0 8 1	3 7 5 1	4 0 2 1	4 0 6 1	4 0 7 1	4 0 9 1	4 0 0 1	3 1 1 1	3 8 3 1	3 8 4 1	3 8 5 1	3 9 1 1	3 9 2 1	3 9 3 1	3 9 4 1	3 9 5 1	3 8 6 1	3 8 8 1	3 8 9 1	4 0 1 1
Genital System (continued)																								
Preputial gland			+																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+																		
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hemangiosarcoma, multiple					X																			
Thymus	+	M	I	M	M	+	I	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																				
Diaphragm, carcinoma, metastatic, pancreas				X																				
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X			X								X
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma																X			X					
Carcinoma, metastatic, liver				X																				
Carcinoma, metastatic, pancreas				X																				
Hepatocellular carcinoma, metastatic, liver			X		X																	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
None																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	4 0 3 1	4 0 4 1	4 0 5 1	3 7 2 1	3 7 3 1	3 7 4 1	3 7 6 1	3 7 7 1	3 7 8 1	3 7 9 1	3 7 0 1	4 8 1 1	4 1 2 1	4 1 3 1	4 1 4 1	4 1 5 1	3 1 7 1	3 9 8 1	3 9 9 1	4 9 0 1	4 0 6 1	4 1 7 1	4 1 8 1	4 1 9 1	4 2 0 1	Total Tissues/ Tumors
Genital System (continued)																										
Preputial gland																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Hemangiosarcoma, multiple																										1
Thymus	+	+	+	+	+	+	M	M	M	+	+	+	M	M	M	+	+	I	+	M	+	+	M	+	+	32
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, carcinoma, metastatic, pancreas																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																								5
Alveolar/bronchiolar adenoma, multiple							X																			1
Alveolar/bronchiolar carcinoma			X																							3
Carcinoma, metastatic, liver																										1
Carcinoma, metastatic, pancreas																										1
Hepatocellular carcinoma, metastatic, liver																		X								4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	49
Special Senses System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	4 0 3 1	4 0 4 1	4 0 5 1	3 7 2 1	3 7 3 1	3 7 4 1	3 7 6 1	3 7 7 1	3 7 8 1	3 7 9 1	3 7 0 1	4 8 1 1	4 1 1 1	4 1 2 1	4 1 3 1	4 1 4 1	4 1 5 1	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 1 6 1	4 1 7 1	4 1 8 1	4 1 9 1	4 2 0 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X																								1
Lymphoma malignant mixed																										1

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

	0 μL	7.5 μL	15 μL	30 μL
Adrenal Cortex: Adenoma				
Overall rate[a]	8/50 (16%)	5/50 (10%)	2/49 (4%)	4/50 (8%)
Adjusted rate[b]	18.6%	12.2%	4.4%	9.3%
Terminal rate[c]	8/43 (19%)	5/41 (12%)	2/45 (4%)	4/43 (9%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test[d]	P=0.110N	P=0.306N	P=0.040N	P=0.177N
Logistic regression test[d]	P=0.110N	P=0.306N	P=0.040N	P=0.175N
Cochran-Armitage test[d]	P=0.120N			
Fisher exact test[d]		P=0.277N	P=0.049N	P=0.178N
Harderian Gland: Adenoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	4.4%	6.5%	0.0%
Terminal rate	0/43 (0%)	0/41 (0%)	3/46 (7%)	0/43 (0%)
First incidence (days)	–[e]	590	730 (T)	–
Life table test	P=0.523N	P=0.229	P=0.134	–
Logistic regression test	P=0.560N	P=0.296	P=0.134	–
Cochran-Armitage test	P=0.531N			
Fisher exact test		P=0.247	P=0.121	–
Liver: Hepatocellular Adenoma				
Overall rate	6/50 (12%)	11/50 (22%)	9/50 (18%)	12/50 (24%)
Adjusted rate	14.0%	26.0%	19.6%	27.9%
Terminal rate	6/43 (14%)	10/41 (24%)	9/46 (20%)	12/43 (28%)
First incidence (days)	730 (T)	576	730 (T)	730 (T)
Life table test	P=0.133	P=0.121	P=0.337	P=0.094
Logistic regression test	P=0.140	P=0.118	P=0.337	P=0.094
Cochran-Armitage test	P=0.123			
Fisher exact test		P=0.143	P=0.288	P=0.096
Liver: Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted rate	9.0%	8.9%	12.8%	14.6%
Terminal rate	3/43 (7%)	1/41 (2%)	5/46 (11%)	3/43 (7%)
First incidence (days)	635	576	714	556
Life table test	P=0.186	P=0.616	P=0.414	P=0.277
Logistic regression test	P=0.170	P=0.623N	P=0.369	P=0.257
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.643N	P=0.370	P=0.262
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	9/50 (18%)	14/50 (28%)	14/50 (28%)	18/50 (36%)
Adjusted rate	20.4%	31.7%	29.8%	38.1%
Terminal rate	8/43 (19%)	11/41 (27%)	13/46 (28%)	14/43 (33%)
First incidence (days)	635	576	714	556
Life table test	P=0.049	P=0.148	P=0.225	P=0.044
Logistic regression test	P=0.040	P=0.144	P=0.206	P=0.034
Cochran-Armitage test	P=0.036			
Fisher exact test		P=0.171	P=0.171	P=0.035

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	5/50 (10%)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Adjusted rate	11.6%	4.9%	14.9%	14.0%
Terminal rate	5/43 (12%)	2/41 (5%)	6/46 (13%)	6/43 (14%)
First incidence (days)	730 (T)	730 (T)	714	730 (T)
Life table test	P=0.274	P=0.236N	P=0.428	P=0.500
Logistic regression test	P=0.275	P=0.236N	P=0.427	P=0.500
Cochran-Armitage test	P=0.262			
Fisher exact test		P=0.218N	P=0.380	P=0.500
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	6/50 (12%)	4/50 (8%)	3/50 (6%)
Adjusted rate	11.6%	14.6%	8.7%	7.0%
Terminal rate	5/43 (12%)	6/41 (15%)	4/46 (9%)	3/43 (7%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test	P=0.212N	P=0.466	P=0.458N	P=0.356N
Logistic regression test	P=0.212N	P=0.466	P=0.458N	P=0.356N
Cochran-Armitage test	P=0.226N			
Fisher exact test		P=0.500	P=0.500N	P=0.357N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	8/50 (16%)	7/50 (14%)	10/50 (20%)	9/50 (18%)
Adjusted rate	18.6%	17.1%	21.3%	20.9%
Terminal rate	8/43 (19%)	7/41 (17%)	9/46 (20%)	9/43 (21%)
First incidence (days)	730 (T)	730 (T)	714	730 (T)
Life table test	P=0.395	P=0.540N	P=0.459	P=0.500
Logistic regression test	P=0.393	P=0.540N	P=0.460	P=0.500
Cochran-Armitage test	P=0.375			
Fisher exact test		P=0.500N	P=0.398	P=0.500
Spleen: Hemangiosarcoma				
Overall rate	6/50 (12%)	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted rate	13.4%	0.0%	10.3%	4.4%
Terminal rate	5/43 (12%)	0/41 (0%)	3/46 (7%)	1/43 (2%)
First incidence (days)	536	–	663	675
Life table test	P=0.225N	P=0.022N	P=0.455N	P=0.138N
Logistic regression test	P=0.238N	P=0.017N	P=0.589N	P=0.141N
Cochran-Armitage test	P=0.234N			
Fisher exact test		P=0.013N	P=0.500N	P=0.134N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.4%	2.4%	6.5%	0.0%
Terminal rate	1/43 (2%)	1/41 (2%)	3/46 (7%)	0/43 (0%)
First incidence (days)	558	730 (T)	730 (T)	–
Life table test	P=0.236N	P=0.516N	P=0.528	P=0.240N
Logistic regression test	P=0.245N	P=0.477N	P=0.412	P=0.272N
Cochran-Armitage test	P=0.242N			
Fisher exact test		P=0.500N	P=0.500	P=0.247N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
All Organs: Hemangiosarcoma				
Overall rate	10/50 (20%)	1/50 (2%)	6/50 (12%)	4/50 (8%)
Adjusted rate	21.9%	2.4%	12.1%	9.0%
Terminal rate	8/43 (19%)	1/41 (2%)	3/46 (7%)	3/43 (7%)
First incidence (days)	536	730 (T)	633	675
Life table test	P=0.140N	P=0.008N	P=0.179N	P=0.080N
Logistic regression test	P=0.153N	P=0.005N	P=0.337N	P=0.080N
Cochran-Armitage test	P=0.146N			
Fisher exact test		P=0.004N	P=0.207N	P=0.074N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	10/50 (20%)	2/50 (4%)	6/50 (12%)	5/50 (10%)
Adjusted rate	21.9%	4.9%	12.1%	11.3%
Terminal rate	8/43 (19%)	2/41 (5%)	3/46 (7%)	4/43 (9%)
First incidence (days)	536	730 (T)	633	675
Life table test	P=0.206N	P=0.021N	P=0.179N	P=0.137N
Logistic regression test	P=0.222N	P=0.016N	P=0.337N	P=0.138N
Cochran-Armitage test	P=0.216N			
Fisher exact test		P=0.014N	P=0.207N	P=0.131N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
Overall rate	3/50 (6%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	7.0%	6.7%	0.0%	6.7%
Terminal rate	3/43 (7%)	1/41 (2%)	0/46 (0%)	1/43 (2%)
First incidence (days)	730 (T)	397	–	698
Life table test	P=0.511N	P=0.638	P=0.110N	P=0.659N
Logistic regression test	P=0.553N	P=0.627N	P=0.110N	P=0.660N
Cochran-Armitage test	P=0.523N			
Fisher exact test		P=0.661N	P=0.121N	P=0.661N
All Organs: Benign Neoplasms				
Overall rate	16/50 (32%)	18/50 (36%)	23/50 (46%)	20/50 (40%)
Adjusted rate	36.2%	40.7%	48.9%	46.5%
Terminal rate	15/43 (35%)	15/41 (37%)	22/46 (48%)	20/43 (47%)
First incidence (days)	558	576	714	730 (T)
Life table test	P=0.237	P=0.356	P=0.168	P=0.261
Logistic regression test	P=0.245	P=0.363	P=0.148	P=0.275
Cochran-Armitage test	P=0.209			
Fisher exact test		P=0.417	P=0.109	P=0.266
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	14/50 (28%)	15/50 (30%)	16/50 (32%)
Adjusted rate	41.1%	29.7%	30.0%	32.7%
Terminal rate	16/43 (37%)	8/41 (20%)	11/46 (24%)	10/43 (23%)
First incidence (days)	536	378	633	556
Life table test	P=0.356N	P=0.265N	P=0.209N	P=0.346N
Logistic regression test	P=0.376N	P=0.166N	P=0.343N	P=0.356N
Cochran-Armitage test	P=0.379N			
Fisher exact test		P=0.198N	P=0.263N	P=0.338N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
All Organs: Benign or Malignant Neoplasms				
Overall rate	27/50 (54%)	26/50 (52%)	33/50 (66%)	29/50 (58%)
Adjusted rate	58.5%	54.2%	66.0%	59.2%
Terminal rate	24/43 (56%)	19/41 (46%)	29/46 (63%)	23/43 (53%)
First incidence (days)	536	378	633	556
Life table test	P=0.361	P=0.553	P=0.288	P=0.434
Logistic regression test	P=0.293	P=0.516N	P=0.152	P=0.417
Cochran-Armitage test	P=0.289			
Fisher exact test		P=0.500N	P=0.154	P=0.420

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the 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 controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Overall Historical Incidence: Dermal (Acetone)			
Total	24/100 (24.0%)	10/100 (10.0%)	32/100 (32.0%)
Standard deviation	17.0%	2.8%	19.8%
Range	12%-36%	8%-12%	18%-46%
Overall Historical Incidence: Feed			
Total	347/1,466 (23.7%)	241/1,466 (16.4%)	531/1,466 (36.2%)
Standard deviation	13.6%	7.0%	14.1%
Range	4%-60%	3%-29%	10%-68%
Overall Historical Incidence: Inhalation			
Total	120/673 (17.8%)	136/673 (20.2%)	241/673 (35.8%)
Standard deviation	11.0%	5.9%	12.1%
Range	4%-38%	9%-29%	11%-56%
Overall Historical Incidence: Water Gavage			
Total	40/315 (12.7%)	39/315 (12.4%)	74/315 (23.5%)
Standard deviation	5.2%	6.1%	7.2%
Range	4%-18%	6%-24%	14%-36%
Overall Historical Incidence: Corn Oil Gavage			
Total	265/951 (27.9%)	163/951 (17.1%)	388/951 (40.8%)
Standard deviation	14.6%	5.7%	15.1%
Range	4%-58%	8%-32%	14%-72%

[a] Data as of 31 March 1993

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

	0 μL	7.5 μL	15 μL	30 μL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		
Moribund	2	3	2	1
Natural deaths	5	4	2	6
Survivors				
Terminal sacrifice	43	41	46	43
Missing		1		
Animals examined microscopically	60	53	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)	(1)	(10)
Necrosis, focal		1 (33%)		
Pancreas	(10)			(10)
Atrophy, focal				1 (10%)
Hypertrophy, focal	1 (10%)			
Endocrine System				
Adrenal cortex	(10)			(10)
Hypertrophy, focal	5 (50%)			4 (40%)
Capsule, hyperplasia	8 (80%)			10 (100%)
Pituitary gland	(10)			(10)
Cyst				1 (10%)
Pars distalis, hyperplasia, focal	1 (10%)			
Nervous System				
Brain	(10)			(10)
Mineralization, focal	10 (100%)			8 (80%)
Respiratory System				
Lung	(10)			(10)
Adenomatosis, focal	1 (10%)			1 (10%)
Inflammation, chronic, focal	1 (10%)			
Urinary System				
Kidney	(10)			(10)
Nephropathy	9 (90%)			7 (70%)
Renal tubule, mineralization, focal	10 (100%)			9 (90%)

[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 Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine small, jejunum	(47)	(49)	(48)	(46)
Hyperplasia, lymphoid	2 (4%)			
Intestine small, ileum	(47)	(48)	(48)	(46)
Congestion	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus		1 (2%)	9 (18%)	3 (6%)
Clear cell focus	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Clear cell focus, multiple		1 (2%)		
Cyst		1 (2%)		
Eosinophilic focus	1 (2%)			2 (4%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage, focal				1 (2%)
Infarct	1 (2%)			
Inflammation, chronic, focal		1 (2%)		3 (6%)
Inflammation, granulomatous			1 (2%)	
Mixed cell focus			1 (2%)	
Necrosis, focal	4 (8%)		2 (4%)	3 (6%)
Bile duct, hyperplasia, focal			1 (2%)	
Centrilobular, necrosis	1 (2%)			
Sinusoid, dilatation	1 (2%)			
Vein, dilatation	1 (2%)			
Mesentery	(2)	(2)	(2)	
Hemorrhage			1 (50%)	
Fat, necrosis	2 (100%)	1 (50%)	1 (50%)	
Pancreas	(50)	(49)	(50)	(50)
Cyst			1 (2%)	
Edema		1 (2%)		
Hemorrhage	1 (2%)			
Inflammation, chronic			1 (2%)	
Vacuolization cytoplasmic		1 (2%)		
Duct, ectasia	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(48)
Hyperkeratosis, focal	1 (2%)			
Hyperplasia, squamous			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(50)	(48)
Erosion				2 (4%)
Inflammation, focal, subacute			1 (2%)	
Tooth				(1)
Abscess				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	2 (4%)	2 (4%)		1 (2%)
Polyarteritis		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Atrophy		1 (2%)		
Hyperplasia			2 (4%)	
Hyperplasia, focal	20 (40%)	23 (47%)	21 (43%)	18 (36%)
Hypertrophy			2 (4%)	2 (4%)
Hypertrophy, focal	13 (26%)	10 (20%)	4 (8%)	9 (18%)
Necrosis				1 (2%)
Capsule, hyperplasia	45 (90%)	44 (90%)	43 (88%)	38 (76%)
Extra adrenal tissue, necrosis	1 (2%)			
Adrenal gland		(2)	(2)	(1)
Corticomedullary junction, degeneration			1 (50%)	1 (100%)
Corticomedullary junction, pigmentation		2 (100%)	1 (50%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Degeneration	1 (2%)			
Fibrosis			1 (2%)	
Hyperplasia			1 (2%)	
Hyperplasia, focal				1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia	1 (2%)			
Pituitary gland	(48)	(47)	(48)	(49)
Cyst	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Pars distalis, hyperplasia, focal	1 (2%)		1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	
Inflammation, chronic, focal			1 (2%)	
Follicle, cyst		1 (2%)	2 (4%)	
Follicular cell, hyperplasia	7 (14%)	9 (18%)	6 (12%)	13 (26%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
2-Year Study (continued)				
Genital System				
Coagulating gland	(1)			(1)
Inflammation	1 (100%)			
Inflammation, suppurative				1 (100%)
Epididymis	(50)	(49)	(50)	(50)
Granuloma sperm	2 (4%)		1 (2%)	1 (2%)
Inflammation, chronic, focal			1 (2%)	
Mineralization		1 (2%)		
Fat, necrosis			2 (4%)	
Head, inflammation, chronic			1 (2%)	
Penis	(1)	(1)		
Inflammation, suppurative		1 (100%)		
Preputial gland	(1)	(1)		(1)
Cyst				1 (100%)
Dilatation	1 (100%)	1 (100%)		
Prostate	(50)	(49)	(50)	(50)
Inflammation, chronic				1 (2%)
Inflammation, subacute	1 (2%)		1 (2%)	1 (2%)
Seminal vesicle	(50)	(49)	(50)	(50)
Inflammation, chronic		1 (2%)		
Testes	(50)	(49)	(50)	(50)
Atrophy			1 (2%)	
Giant cell		2 (4%)		2 (4%)
Hypospermia			1 (2%)	
Interstitial cell, hyperplasia, focal		1 (2%)	1 (2%)	
Seminiferous tubule, degeneration	2 (4%)	5 (10%)	2 (4%)	5 (10%)
Seminiferous tubule, mineralization		1 (2%)	1 (2%)	1 (2%)
Tunic, mineralization	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(50)
Sternal, myelofibrosis	1 (2%)			
Lymph node, mesenteric	(47)	(50)	(47)	(50)
Congestion		1 (2%)	1 (2%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, chronic				1 (2%)
Sinus, congestion	2 (4%)			
Spleen	(50)	(50)	(50)	(50)
Fibrosis, focal	1 (2%)			
Hematopoietic cell proliferation	45 (90%)	45 (90%)	46 (92%)	47 (94%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Capsule, inflammation			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Acanthosis	1 (2%)			
Edema				1 (2%)
Exudate	2 (4%)			
Inflammation, chronic, focal			1 (2%)	
Pigmentation, melanin	1 (2%)			
Ulcer	1 (2%)			
Control, edema			1 (2%)	
Control, infiltration cellular, focal, mast cell			1 (2%)	
Head, exudate		1 (2%)		
Subcutaneous tissue, granuloma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(48)	(50)	(50)
Femur, fracture			1 (2%)	
Skeletal muscle		(1)	(1)	(1)
Diaphragm, inflammation, chronic			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage		2 (4%)		
Mineralization, focal	40 (80%)	41 (82%)	46 (92%)	41 (82%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenomatosis, focal		1 (2%)	1 (2%)	
Congestion	1 (2%)	1 (2%)	2 (4%)	6 (12%)
Hemorrhage, focal				1 (2%)
Inflammation, chronic				1 (2%)
Inflammation, chronic, focal	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Necrosis, focal	1 (2%)			
Alveolar epithelium, hyperplasia, focal	2 (4%)		4 (8%)	6 (12%)
Alveolus, infiltration cellular, histiocyte	2 (4%)	3 (6%)	1 (2%)	
Peribronchial, hyperplasia, lymphoid	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Special Senses System				
Ear			(1)	
Ulcer			1 (100%)	
Eye		(1)		
Cornea, necrosis		1 (100%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Hyperplasia, tubular			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, suppurative				1 (2%)
Metaplasia, focal, osseous			1 (2%)	1 (2%)
Nephropathy	40 (80%)	41 (82%)	44 (88%)	37 (74%)
Capsule, inflammation, chronic			1 (2%)	
Cortex, atrophy, focal		2 (4%)	1 (2%)	1 (2%)
Cortex, cyst	3 (6%)		2 (4%)	4 (8%)
Cortex, metaplasia, focal, osseous		1 (2%)		
Pelvis, dilatation			2 (4%)	
Perirenal tissue, necrosis			1 (2%)	
Renal tubule, mineralization, focal	37 (74%)	40 (80%)	33 (66%)	29 (58%)
Urinary bladder	(50)	(49)	(50)	(50)
Hemorrhage, focal				1 (2%)
Inflammation, chronic				1 (2%)

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

TABLE D1	Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate	187
TABLE D2	Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate	192
TABLE D3	Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate	214
TABLE D4	Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice	219
TABLE D5	Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate	220

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

	0 μL	7.5 μL	15 μL	30 μL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	10
Early deaths				
Accidental deaths				1
Moribund	4	5	5	8
Natural deaths	5	8	7	5
Survivors				
Died last week of study		1	1	
Terminal sacrifice	41	37	36	36
Missing			1	
Animals examined microscopically	60	55	53	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(4)	(3)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma	3 (30%)			1 (10%)
Integumentary System				
Skin	(10)			(10)
Abdominal, mast cell tumor benign	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(4)	(3)	(10)
Lymphoma malignant lymphocytic	1 (10%)			1 (10%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
2-Year Study				
Alimentary System				
Gallbladder	(47)	(41)	(44)	(45)
Intestine large, cecum	(48)	(45)	(48)	(50)
Leiomyoma			1 (2%)	
Intestine small, duodenum	(47)	(45)	(48)	(48)
Intestine small, jejunum	(48)	(44)	(50)	(48)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(47)	(44)	(49)	(47)
Liver	(50)	(51)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma		1 (2%)	1 (2%)	
Hemangiosarcoma, metastatic, spleen				1 (2%)
Hepatocellular carcinoma	4 (8%)	5 (10%)	6 (12%)	2 (4%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular adenoma	3 (6%)	10 (20%)	13 (26%)	9 (18%)
Hepatocellular adenoma, multiple	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma		3 (6%)	1 (2%)	
Pancreas	(49)	(51)	(50)	(49)
Salivary glands	(50)	(51)	(50)	(50)
Stomach, forestomach	(50)	(51)	(50)	(49)
Squamous cell carcinoma		2 (4%)		
Squamous cell papilloma	1 (2%)			2 (4%)
Tongue				(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Heart	(50)	(51)	(50)	(50)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(51)	(50)	(50)
Adenoma	2 (4%)		1 (2%)	1 (2%)
Capsule, adenoma		1 (2%)		
Adrenal medulla	(50)	(51)	(50)	(50)
Pheochromocytoma benign	4 (8%)			
Islets, pancreatic	(50)	(51)	(50)	(49)
Carcinoma	2 (4%)			
Pituitary gland	(49)	(48)	(50)	(49)
Pars distalis, adenoma	6 (12%)	4 (8%)	4 (8%)	1 (2%)
Thyroid gland	(50)	(51)	(50)	(50)
Follicular cell, adenoma	1 (2%)	5 (10%)	1 (2%)	1 (2%)
Follicular cell, carcinoma		1 (2%)		
General Body System				
Tissue NOS	(1)	(1)	(2)	(1)
Hemangiosarcoma	1 (100%)	1 (100%)	2 (100%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Genital System				
Ovary	(49)	(51)	(49)	(49)
Cystadenoma	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Granulosa cell tumor malignant	1 (2%)		1 (2%)	
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (2%)		
Luteoma			1 (2%)	
Teratoma malignant	1 (2%)			
Uterus	(50)	(51)	(49)	(50)
Hemangiosarcoma			1 (2%)	
Polyp	3 (6%)		1 (2%)	
Polyp, multiple		1 (2%)		
Sarcoma stromal	1 (2%)			
Cervix, histiocytic sarcoma		2 (4%)	1 (2%)	
Cervix, leiomyosarcoma			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(51)	(50)	(50)
Lymph node	(7)	(7)	(5)	(7)
Sarcoma, metastatic, tissue NOS		1 (14%)		
Axillary, sarcoma, metastatic, tissue NOS		1 (14%)		
Mediastinal, histiocytic sarcoma		1 (14%)		
Lymph node, mandibular	(46)	(47)	(47)	(47)
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(49)	(45)	(48)	(50)
Histiocytic sarcoma		1 (2%)		
Spleen	(50)	(51)	(50)	(50)
Hemangiosarcoma			3 (6%)	2 (4%)
Hemangiosarcoma, multiple				1 (2%)
Thymus	(41)	(40)	(35)	(45)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Integumentary System				
Mammary gland	(49)	(46)	(50)	(44)
Carcinoma	1 (2%)			
Skin	(50)	(51)	(50)	(50)
Basal cell carcinoma				1 (2%)
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)		1 (2%)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Subcutaneous tissue, sarcoma		2 (4%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(51)	(50)	(50)
Vertebra, osteosarcoma				1 (2%)
Skeletal muscle	(1)	(1)	(1)	(4)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Nervous System				
Brain	(50)	(51)	(50)	(50)
Respiratory System				
Lung	(50)	(51)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland			1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)	6 (12%)	4 (8%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	
Carcinoma, metastatic, mammary gland	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	2 (4%)	4 (8%)	3 (6%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)	1 (2%)	
Osteosarcoma, metastatic, bone				1 (2%)
Teratoma malignant, metastatic	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Ear		(1)	(1)	
Fibrosarcoma		1 (100%)	1 (100%)	
Harderian gland	(1)	(1)	(5)	
Adenocarcinoma			1 (20%)	
Adenoma	1 (100%)	1 (100%)	4 (80%)	
Urinary System				
Kidney	(50)	(51)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Ureter	(1)	(1)		
Urinary bladder	(49)	(47)	(49)	(48)
Systemic Lesions				
Multiple organs	(50)	(51)	(50)	(50)
Histiocytic sarcoma		3 (6%)	1 (2%)	
Leukemia lymphocytic	1 (2%)			
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Lymphoma malignant mixed	5 (10%)	8 (16%)	5 (10%)	6 (12%)
Lymphoma malignant undifferentiated cell		1 (2%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	5		3	
2-Year study	31	41	38	28
Total primary neoplasms				
15-Month interim evaluation	5		3	
2-Year study	50	69	62	39
Total animals with benign neoplasms				
15-Month interim evaluation	4		1	
2-Year study	20	26	26	16
Total benign neoplasms				
15-Month interim evaluation	4		1	
2-Year study	28	34	33	19
Total animals with malignant neoplasms				
15-Month interim evaluation	1		2	
2-Year study	17	27	23	18
Total malignant neoplasms				
15-Month interim evaluation	1		2	
2-Year study	22	35	29	20
Total animals with metastatic neoplasms				
2-Year study	5	5	5	2
Total metastatic neoplasms				
2-Year study	8	6	5	2

[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 Diethylphthalate: 0 μL

Number of Days on Study	1 9 3	5 9 1	6 2 0	6 6 2	6 6 3	6 6 5	6 7 5	7 2 4	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 8 8 1	0 7 6 1	1 0 1 1	0 7 7 1	0 7 5 1	1 0 6 1	1 1 8 1	0 9 9 1	0 7 1 1	0 9 6 1	0 9 7 1	0 9 8 1	1 0 0 1	1 0 7 1	1 0 8 1	1 0 9 1	1 1 0 1	0 8 6 1	0 8 7 1	0 8 9 1	0 9 0 1	1 1 1 1	1 1 2 1	1 1 3 1	1 1 4 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	A	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma		X	X																					X	
Hepatocellular adenoma														X											
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X		X									
Adrenal gland	+		+					+	+	+	+	+	+	+	+		+		+	+		+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X						X											X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X				X				X									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma							X																		
General Body System																									
Tissue NOS													+												
Hemangiosarcoma													X												

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 1 5 1	0 7 2 1	0 7 3 1	0 7 4 1	0 8 1 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 5 1	1 0 2 1	1 0 3 1	1 0 4 1	1 0 5 1	0 7 8 1	0 7 9 1	0 8 0 1	1 1 6 1	1 1 7 1	1 1 9 1	1 2 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X																						1
Hepatocellular carcinoma											X															4
Hepatocellular adenoma											X			X												3
Hepatocellular adenoma, multiple																						X				1
Hepatocholangiocarcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Adrenal gland	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+		+		38
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																				X						6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS																										1
Hemangiosarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	1 9 3	5 9 1	6 2 0	6 6 2	6 6 3	6 6 5	6 7 5	7 2 4	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 8 8 1	0 7 6 1	1 0 1 1	0 7 7 1	0 7 5 1	1 0 6 1	1 1 8 1	0 9 9 1	0 7 1 1	0 9 6 1	0 9 7 1	0 9 8 1	0 9 0 1	1 0 0 1	1 0 7 1	1 0 8 1	1 0 9 1	1 1 0 1	1 8 6 1	1 8 7 1	1 8 9 1	1 9 0 1	1 1 1 1	1 1 2 1	1 1 3 1	1 1 4 1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																	X						X		
Granulosa cell tumor malignant																									
Teratoma malignant	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp				X		X														X					
Sarcoma stromal					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+						+		+	+					+				
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	M	I	M	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																							
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma									X									X							
Carcinoma, metastatic, mammary gland							X																		
Hepatocellular carcinoma, metastatic, liver			X																						
Hepatocholangiocarcinoma, metastatic, liver		X																							
Teratoma malignant, metastatic	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 1 5 1	0 7 2 1	0 7 3 1	0 7 4 1	0 8 1 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 5 1	1 0 2 1	1 0 3 1	1 0 4 1	1 1 5 1	1 0 8 1	0 7 9 1	0 7 0 1	0 8 6 1	1 1 7 1	1 1 9 1	1 2 0 1	Total Tissues/ Tumors
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Cystadenoma														X												3
Granulosa cell tumor malignant																			X							1
Teratoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp																										3
Sarcoma stromal																										1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+												7
Lymph node, mandibular	+	+	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	41
Hepatocholangiocarcinoma, metastatic, liver																										1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma											X															1
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X												X				2
Alveolar/bronchiolar carcinoma																										2
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver											X															2
Hepatocholangiocarcinoma, metastatic, liver																										1
Teratoma malignant, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	1	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	9	2	6	6	6	7	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	1	0	2	3	5	5	4	7	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2
Carcass ID Number	0	0	1	0	0	1	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	1	1
	8	7	0	7	7	0	1	9	7	9	9	9	0	0	0	0	1	8	8	8	9	1	1	1	1
	8	6	1	7	5	6	8	9	1	6	7	8	0	7	8	9	0	6	7	9	0	1	2	3	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter								+																	
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia lymphocytic								X																	
Lymphoma malignant lymphocytic								X																	
Lymphoma malignant mixed				X									X		X					X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 0 μL (continued)

Number of Days on Study	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 1 5 1	0 7 2 1	0 7 3 1	0 7 4 1	0 8 1 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 5 1	0 9 6 1	1 0 2 1	1 0 3 1	1 0 4 1	1 0 5 1	0 7 8 1	0 7 9 1	0 8 0 1	1 1 6 1	1 1 7 1	1 1 9 1	1 2 0 1	Total Tissues/ Tumors
Special Senses System																											
Eye																								+		1
Harderian gland																								+		1
Adenoma																								X		1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia lymphocytic																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed														X													5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL

Number of Days on Study	2 7 3	3 6 5	4 8 1	4 8 4	5 0 9	5 6 0	5 6 3	5 9 7	6 6 8	6 7 5	6 7 8	6 8 2	7 1 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 9 5 1	1 8 2 1	2 2 7 1	2 0 6 1	2 0 5 1	2 2 6 1	1 9 3 1	2 1 5 1	1 9 4 1	2 1 8 1	2 3 3 1	2 3 5 1	2 0 1 1	1 9 1 1	1 9 2 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 5 1	1 9 6 1	1 9 7 1	1 9 8 1	1 9 9 1	2 0 0 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	A	+	A	A	A	+	A	+	+	+	+	M	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large, cecum	+	+	A	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	A	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	A	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma						X	X					X			X									
Hepatocellular adenoma										X				X		X								
Hepatocellular adenoma, multiple																				X				
Histiocytic sarcoma				X												X					X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								
Adrenal gland	+	+	+		+		+		+		+		+	+	+	+	+	+		+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													X					X		X				
Follicular cell, carcinoma																								
General Body System																								
Tissue NOS																								
Hemangiosarcoma																								
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																			X					
Histiocytic sarcoma				X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 0 7 1	2 0 8 1	2 0 9 1	2 1 0 1	2 2 0 8 1	2 0 2 1	2 0 3 1	2 0 4 1	2 2 9 1	2 3 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 3 1 1	2 3 2 1	2 3 4 1	2 1 6 1	2 1 7 1	2 1 9 1	2 2 0 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	2 4 0 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma														X													1
Hepatocellular carcinoma					X																						5
Hepatocellular adenoma			X		X			X			X								X			X	X				10
Hepatocellular adenoma, multiple																					X						2
Histiocytic sarcoma																											3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma													X														2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Capsule, adenoma				X																							1
Adrenal gland	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma			X			X									X												4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma	X																					X					5
Follicular cell, carcinoma															X												1
General Body System																											
Tissue NOS																									+		1
Hemangiosarcoma																									X		1
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma				X								X							X								4
Histiocytic sarcoma																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	2 7 3	3 6 5	4 8 1	4 8 4	5 0 9	5 6 0	5 6 3	5 9 7	6 6 8	6 7 5	6 7 8	6 8 2	7 1 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 9 5 1	1 8 2 1	2 2 7 1	2 0 6 1	2 0 5 1	2 2 6 1	1 9 3 1	2 1 5 1	1 9 4 1	2 1 8 1	2 3 3 1	2 3 5 1	2 0 1 1	1 9 1 1	1 9 2 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 5 1	1 9 6 1	1 9 7 1	1 9 8 1	1 9 9 1	2 0 0 1
Genital System (continued)																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp, multiple																								X
Cervix, histiocytic sarcoma				X																	X			
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+	+	+					+							
Sarcoma, metastatic, tissue NOS										X														
Axillary, sarcoma, metastatic, tissue NOS										X														
Mediastinal, histiocytic sarcoma																	X							
Lymph node, mandibular	+	+	I	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X							
Lymph node, mesenteric	+	+	I	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M
Histiocytic sarcoma																	X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	I	I	I	M	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	M
Integumentary System																								
Mammary gland	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma					X																			
Subcutaneous tissue, fibrous histiocytoma																								
Subcutaneous tissue, sarcoma		X								X														
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																							
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																		
Alveolar/bronchiolar carcinoma			X		X						X													
Hepatocellular carcinoma, metastatic, liver						X	X					X												
Histiocytic sarcoma																	X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Fibrosarcoma																								
Harderian gland																+								
Adenoma																X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 0 7 1	2 0 8 1	2 0 9 1	2 1 0 1	2 2 8 1	2 0 2 1	2 0 3 1	2 0 4 1	2 2 9 1	2 3 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 3 1 1	2 3 2 1	2 3 4 1	2 1 6 1	2 1 7 1	2 1 9 1	2 2 0 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	2 4 0 1	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp, multiple																										1
Cervix, histiocytic sarcoma																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																							+	+		7
Sarcoma, metastatic, tissue NOS																										1
Axillary, sarcoma, metastatic, tissue NOS																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	M	40
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibrosarcoma																			X							2
Subcutaneous tissue, fibrous histiocytoma																					X					1
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma						X	X	X							X						X					6
Alveolar/bronchiolar carcinoma																										3
Hepatocellular carcinoma, metastatic, liver					X																					4
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Ear																					+					1
Fibrosarcoma																					X					1
Harderian gland																										1
Adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	2 7 3	3 6 5	4 8 1	4 8 4	5 0 9	5 6 0	5 6 3	5 9 7	6 6 8	6 7 5	6 7 8	6 8 2	7 1 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 9 5 1	1 8 2 1	2 2 7 1	2 0 6 1	2 0 5 1	2 2 6 1	1 9 3 1	2 1 5 1	1 9 4 1	2 1 8 1	2 3 3 1	2 3 5 1	2 0 1 1	1 9 1 1	1 9 2 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 5 1	1 9 6 1	1 9 7 1	1 9 8 1	1 9 9 1	2 0 0 1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Ureter																									
Urinary bladder	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X													X					X			
Lymphoma malignant histiocytic																	X								
Lymphoma malignant lymphocytic	X										X														
Lymphoma malignant mixed								X				X												X	
Lymphoma malignant undifferentiated cell type																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 7.5 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	2 0 7 1	2 0 8 1	2 0 9 1	2 1 0 1	2 2 8 1	2 0 2 1	2 0 3 1	2 0 4 1	2 2 9 1	2 3 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 3 1 1	2 3 2 1	2 3 4 1	2 1 6 1	2 1 7 1	2 1 9 1	2 2 0 1	2 3 6 1	2 3 7 1	2 3 8 1	2 3 9 1	2 4 0 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Ureter																							+			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										3
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic													X													3
Lymphoma malignant mixed														X					X				X	X	X	8
Lymphoma malignant undifferentiated cell type																				X						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL

Number of Days on Study	1 9 3	3 9 3	5 2 1	5 6 8	5 8 3	5 8 6	6 3 2	6 4 4	6 5 3	6 6 1	6 7 3	6 7 5	7 0 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 2	7 3 2
Carcass ID Number	3 4 0 1	3 3 9 1	3 1 5 1	3 2 4 1	3 1 2 1	3 2 7 1	3 3 2 1	3 1 1 1	3 1 9 1	3 6 0 1	3 4 2 1	3 2 9 1	3 4 3 1	3 1 6 1	3 1 7 1	3 1 8 1	3 2 0 1	3 5 1 1	3 5 2 1	3 5 3 1	3 5 4 1	3 5 5 1	3 5 9 1	3 2 6 1	3 2 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma				X																					
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X													
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Hepatocellular carcinoma								X		X	X	X													
Hepatocellular adenoma						X				X				X			X	X	X		X				
Hepatocellular adenoma, multiple																								X	
Histiocytic sarcoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland			+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X											X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																						X			
General Body System																									
Tissue NOS												+						+							
Hemangiosarcoma												X						X							
Genital System																									
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor malignant																	X								
Luteoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 3 0 1	3 6 1	3 7 1	3 8 1	3 5 6 1	3 5 7 1	3 5 8 1	3 2 1 1	3 2 2 1	3 2 3 1	3 2 5 1	3 4 1 1	3 4 4 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 4 9 1	3 5 0 1	3 1 3 1	3 1 4 1	3 3 1 1	3 3 3 1	3 3 4 1	3 3 5 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																									1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Hepatocellular carcinoma								X											X						6
Hepatocellular adenoma					X	X			X	X											X		X		13
Hepatocellular adenoma, multiple																									1
Histiocytic sarcoma																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																					1
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	46
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X										X														4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																									1
General Body System																									
Tissue NOS																									2
Hemangiosarcoma																									2
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma	X									X															2
Granulosa cell tumor malignant																									1
Luteoma																X									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	1 9 3	3 9 3	5 2 1	5 6 8	5 8 3	5 8 6	6 3 2	6 4 4	6 5 3	6 6 1	6 7 3	6 7 5	7 0 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 2	7 3 2
Carcass ID Number	3 4 0 1	3 3 9 1	3 1 5 1	3 2 4 1	3 1 2 1	3 2 7 1	3 3 2 1	3 1 1 1	3 1 9 1	3 6 0 1	3 4 2 1	3 2 9 1	3 4 3 1	3 1 6 1	3 1 7 1	3 1 8 1	3 2 0 1	3 5 1 1	3 5 2 1	3 5 3 1	3 5 4 1	3 5 5 1	3 5 9 1	3 2 6 1	3 2 8 1
Genital System (continued)																								
Uterus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Polyp																								
Cervix, histiocytic sarcoma						X																		
Cervix, leiomyosarcoma					X																			
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+									+			+								
Lymph node, mandibular	+	+	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X						X		X				
Thymus	+	+	+	M	M	I	+	+	+	M	M	M	+	+	+	+	+	M	M	+	M	M	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord												+										+		
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																								
Alveolar/bronchiolar adenoma			X													X								
Alveolar/bronchiolar carcinoma																								
Alveolar/bronchiolar carcinoma, multiple							X																	
Hepatocellular carcinoma, metastatic, liver											X													
Histiocytic sarcoma						X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear		+																						
Fibrosarcoma		X																						
Eye																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 3 0 1	3 6 1	3 7 1	3 8 1	3 5 6 1	3 5 7 1	3 5 8 1	3 2 1 1	3 2 2 1	3 2 3 1	3 2 5 1	3 4 1 1	3 4 4 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 4 9 1	3 5 0 1	3 1 3 1	3 1 4 1	3 3 1 1	3 3 3 1	3 3 4 1	3 3 5 1	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma												X														1
Polyp																										1
Cervix, histiocytic sarcoma																										1
Cervix, leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+					+														5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	M	+	+	+	35
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																					+					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland													X													1
Alveolar/bronchiolar adenoma																X									X	4
Alveolar/bronchiolar carcinoma				X																						1
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver									X										X							3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Fibrosarcoma																										1
Eye													+													1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	1	3	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	9	9	2	6	8	8	3	4	5	6	7	7	0	3	3	3	3	3	3	3	3	3	3	3
	3	3	1	8	3	6	2	4	3	1	3	5	8	0	0	0	0	0	0	0	0	1	2	2
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	3	1	2	1	2	3	1	1	6	4	2	4	1	1	1	2	5	5	5	5	5	2	2
	0	9	5	4	2	7	2	1	9	0	2	9	3	6	7	8	0	1	2	3	4	5	6	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System (continued)																								
Harderian gland																						+		+
Adenocarcinoma																								
Adenoma																						X		X
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Lymphoma malignant lymphocytic																X								
Lymphoma malignant mixed				X					X				X								X			
Lymphoma malignant undifferentiated cell type										X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 15 μL (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	3 3 0 1	3 6 1	3 7 1	3 8 1	3 6 1	3 7 1	3 8 1	3 1 1	3 2 1	3 3 1	3 5 1	4 1 1	4 4 1	4 5 1	4 6 1	4 7 1	4 8 1	4 9 1	5 0 1	1 3 1	1 4 1	3 1 1	3 3 1	3 4 1	3 5 1	Total Tissues/ Tumors
Special Senses System (continued)																									
Harderian gland						+							+								+				5
Adenocarcinoma													X												1
Adenoma						X															X				4
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Lymphoma malignant lymphocytic						X																			2
Lymphoma malignant mixed							X																		5
Lymphoma malignant undifferentiated cell type																									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL

Number of Days on Study	2 4 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	4 5 2 3 3 4 4 4 9 9 9 1 1 2 3 3 3 3 3 3 3 3 3 3 3
	7 6 1 3 6 5 5 8 1 3 3 2 2 5 0 0 0 0 0 0 0 0 1 1
Carcass ID Number	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
	7 7 5 4 3 6 8 7 5 4 5 3 6 6 4 4 4 4 5 6 6 6 6 6 6
	3 4 8 1 2 0 0 2 4 2 6 3 5 6 6 7 8 9 0 1 2 3 4 7 8
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ +
Gallbladder	+ + + + A + + + A + + + A + + + + + + + + + + + +
Intestine large, colon	+ +
Intestine large, rectum	+ +
Intestine large, cecum	+ +
Intestine small, duodenum	+ + + + A + + + A + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ + + + A + + + A + + + + + + + + + + + + + + + +
Intestine small, ileum	+ + + + A + + + A + + A + + + + + + + + + + + + +
Liver	+ +
Hemangiosarcoma, metastatic, spleen	X
Hepatocellular carcinoma	X X
Hepatocellular carcinoma, multiple	X
Hepatocellular adenoma	X X X X X
Hepatocellular adenoma, multiple	X
Mesentery	+ +
Pancreas	+ I + + + +
Salivary glands	+ +
Stomach, forestomach	+ + + + A +
Squamous cell papilloma	
Stomach, glandular	+ +
Tongue	
Squamous cell papilloma	
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adenoma	
Adrenal gland	+ +
Adrenal medulla	+ +
Islets, pancreatic	+ M + + + +
Parathyroid gland	+ +
Pituitary gland	+ + + + + + + + + + + + + + + + + + M + + + + + +
Pars distalis, adenoma	
Thyroid gland	+ +
Follicular cell, adenoma	X
General Body System	
Tissue NOS	+
Genital System	
Ovary	+ + + + M +
Cystadenoma	X
Hemangiosarcoma	X
Uterus	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	
Carcass ID Number	4 6 9 1	4 7 0 1	4 7 1 1	4 7 5 1	4 7 6 1	4 7 7 1	4 7 8 1	4 7 9 1	4 4 6 1	4 3 7 1	4 3 8 1	4 3 9 1	4 4 0 1	4 3 1 1	4 3 4 1	4 3 5 1	4 4 3 1	4 4 4 1	4 4 5 1	4 5 1 1	4 5 2 1	4 5 3 1	4 5 5 1	4 5 7 1	4 5 9 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																									1
Hepatocellular carcinoma																									2
Hepatocellular carcinoma, multiple																									1
Hepatocellular adenoma	X	X								X										X				X	9
Hepatocellular adenoma, multiple																									1
Mesentery									+																3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																		X				X			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+																								1
Squamous cell papilloma	X																								1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X												1
Adrenal gland	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	39
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																						X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																									1
General Body System																									
Tissue NOS																									1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																			X						2
Hemangiosarcoma																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	247	456	521	633	636	645	645	648	691	693	693	712	712	725	730	730	730	730	730	730	730	730	730	731	731
Carcass ID Number	4731	4741	4581	4411	4321	4601	4801	4721	4541	4421	4561	4331	4651	4661	4461	4471	4481	4491	4501	4611	4621	4631	4641	4671	4681
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+			+					+	+								+			
Lymph node, mandibular	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X						X													
Hemangiosarcoma, multiple							X																		
Thymus	+	I	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	M	A	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma		X																							
Skeletal muscle			+		+		+	+																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+						+																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Osteosarcoma, metastatic, bone		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed									X				X	X								X			X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diethylphthalate: 30 μL (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	
Carcass ID Number	4 6 9 1	4 7 0 1	4 7 1 1	4 7 5 1	4 7 6 1	4 7 7 1	4 7 8 1	4 7 9 1	4 3 6 1	4 3 7 1	4 3 8 1	4 3 9 1	4 4 0 1	4 3 1 1	4 3 4 1	4 3 5 1	4 4 3 1	4 4 4 1	4 4 5 1	4 5 1 1	4 5 2 1	4 5 3 1	4 5 5 1	4 5 7 1	4 5 9 1	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+															7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									2
Hemangiosarcoma, multiple																									1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																									
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																X									1
Squamous cell carcinoma																				X					1
Subcutaneous tissue, fibrosarcoma																									1
Subcutaneous tissue, sarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																									1
Skeletal muscle																									4
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																									2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X														1
Alveolar/bronchiolar carcinoma																									1
Osteosarcoma, metastatic, bone																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																									1
Lymphoma malignant mixed														X											6

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

	0 μL	7.5 μL	15 μL	30 μL
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	0/51 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate[b]	9.3%	0.0%	0.0%	0.0%
Terminal rate[c]	3/41 (7%)	0/38 (0%)	0/37 (0%)	0/36 (0%)
First incidence (days)	662	–[e]	–	–
Life table test[d]	P=0.026N	P=0.076N	P=0.081N	P=0.082N
Logistic regression test[d]	P=0.022N	P=0.066N	P=0.067N	P=0.065N
Cochran-Armitage test[d]	P=0.020N			
Fisher exact test[d]		P=0.056N	P=0.059N	P=0.059N
Harderian Gland: Adenoma				
Overall rate	1/50 (2%)	1/51 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.4%	2.6%	10.8%	0.0%
Terminal rate	1/41 (2%)	1/38 (3%)	4/37 (11%)	0/36 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	–
Life table test	P=0.488N	P=0.745	P=0.150	P=0.526N
Logistic regression test	P=0.488N	P=0.745	P=0.150	P=0.526N
Cochran-Armitage test	P=0.447N			
Fisher exact test		P=0.748N	P=0.181	P=0.500N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/51 (2%)	5/50 (10%)	0/50 (0%)
Adjusted rate	2.4%	2.6%	13.5%	0.0%
Terminal rate	1/41 (2%)	1/38 (3%)	5/37 (14%)	0/36 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	–
Life table test	P=0.522N	P=0.745	P=0.081	P=0.526N
Logistic regression test	P=0.522N	P=0.745	P=0.081	P=0.526N
Cochran-Armitage test	P=0.477N			
Fisher exact test		P=0.748N	P=0.102	P=0.500N
Liver: Hepatocellular Adenoma				
Overall rate	4/50 (8%)	12/51 (24%)	14/50 (28%)	10/50 (20%)
Adjusted rate	9.8%	30.6%	35.5%	24.8%
Terminal rate	4/41 (10%)	11/38 (29%)	12/37 (32%)	7/36 (19%)
First incidence (days)	730 (T)	675	586	456
Life table test	P=0.089	P=0.019	P=0.005	P=0.051
Logistic regression test	P=0.127	P=0.017	P=0.006	P=0.075
Cochran-Armitage test	P=0.137			
Fisher exact test		P=0.030	P=0.009	P=0.074
Liver: Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	5/51 (10%)	6/50 (12%)	3/50 (6%)
Adjusted rate	8.8%	11.7%	14.4%	7.1%
Terminal rate	2/41 (5%)	2/38 (5%)	2/37 (5%)	0/36 (0%)
First incidence (days)	591	560	644	645
Life table test	P=0.450N	P=0.449	P=0.313	P=0.539N
Logistic regression test	P=0.297N	P=0.603	P=0.457	P=0.484N
Cochran-Armitage test	P=0.405N			
Fisher exact test		P=0.513	P=0.370	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	7/50 (14%)	16/51 (31%)	19/50 (38%)	12/50 (24%)
Adjusted rate	15.8%	37.8%	45.0%	28.6%
Terminal rate	5/41 (12%)	12/38 (32%)	14/37 (38%)	7/36 (19%)
First incidence (days)	591	560	586	456
Life table test	P=0.171	P=0.022	P=0.004	P=0.116
Logistic regression test	P=0.231	P=0.029	P=0.005	P=0.161
Cochran-Armitage test	P=0.235			
Fisher exact test		P=0.032	P=0.006	P=0.154
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	6/51 (12%)	4/50 (8%)	1/50 (2%)
Adjusted rate	4.9%	15.0%	10.0%	2.8%
Terminal rate	2/41 (5%)	5/38 (13%)	3/37 (8%)	1/36 (3%)
First incidence (days)	730 (T)	560	521	730 (T)
Life table test	P=0.280N	P=0.114	P=0.298	P=0.545N
Logistic regression test	P=0.238N	P=0.128	P=0.341	P=0.545N
Cochran-Armitage test	P=0.236N			
Fisher exact test		P=0.141	P=0.339	P=0.500N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	3/51 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	4.8%	6.5%	4.9%	2.8%
Terminal rate	1/41 (2%)	0/38 (0%)	1/37 (3%)	1/36 (3%)
First incidence (days)	727	481	632	730 (T)
Life table test	P=0.341N	P=0.474	P=0.656	P=0.548N
Logistic regression test	P=0.308N	P=0.569	P=0.691	P=0.539N
Cochran-Armitage test	P=0.315N			
Fisher exact test		P=0.509	P=0.691N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	9/51 (18%)	6/50 (12%)	2/50 (4%)
Adjusted rate	9.5%	20.6%	14.7%	5.6%
Terminal rate	3/41 (7%)	5/38 (13%)	4/37 (11%)	2/36 (6%)
First incidence (days)	727	481	521	730 (T)
Life table test	P=0.192N	P=0.102	P=0.317	P=0.401N
Logistic regression test	P=0.145N	P=0.143	P=0.370	P=0.393N
Cochran-Armitage test	P=0.149N			
Fisher exact test		P=0.125	P=0.370	P=0.339N
Ovary: Cystadenoma				
Overall rate	3/49 (6%)	4/51 (8%)	2/49 (4%)	2/49 (4%)
Adjusted rate	7.5%	10.5%	5.4%	5.4%
Terminal rate	3/40 (8%)	4/38 (11%)	2/37 (5%)	1/36 (3%)
First incidence (days)	730 (T)	730 (T)	730 (T)	725
Life table test	P=0.365N	P=0.472	P=0.536N	P=0.550N
Logistic regression test	P=0.359N	P=0.472	P=0.536N	P=0.540N
Cochran-Armitage test	P=0.324N			
Fisher exact test		P=0.523	P=0.500N	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	6/49 (12%)	4/48 (8%)	4/50 (8%)	1/49 (2%)
Adjusted rate	13.9%	10.6%	10.0%	2.9%
Terminal rate	4/41 (10%)	3/36 (8%)	3/37 (8%)	1/35 (3%)
First incidence (days)	675	682	521	730 (T)
Life table test	P=0.068N	P=0.445N	P=0.436N	P=0.088N
Logistic regression test	P=0.047N	P=0.237N	P=0.362N	P=0.066N
Cochran-Armitage test	P=0.045N			
Fisher exact test		P=0.383N	P=0.357N	P=0.056N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	4/51 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	2.4%	8.8%	0.0%	4.4%
Terminal rate	1/41 (2%)	1/38 (3%)	0/37 (0%)	0/36 (0%)
First incidence (days)	730 (T)	365	–	633
Life table test	P=0.595N	P=0.172	P=0.520N	P=0.475
Logistic regression test	P=0.579N	P=0.229	P=0.520N	P=0.510
Cochran-Armitage test	P=0.580N			
Fisher exact test		P=0.187	P=0.500N	P=0.500
Spleen: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/51 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	7.8%	6.9%
Terminal rate	0/41 (0%)	0/38 (0%)	2/37 (5%)	0/36 (0%)
First incidence (days)	–	–	675	645
Life table test	P=0.032	–	P=0.105	P=0.113
Logistic regression test	P=0.034	–	P=0.113	P=0.125
Cochran-Armitage test	P=0.034			
Fisher exact test		–	P=0.121	P=0.121
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	5/51 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.3%	12.8%	2.7%	2.8%
Terminal rate	0/41 (0%)	4/38 (11%)	1/37 (3%)	1/36 (3%)
First incidence (days)	675	718	730 (T)	730 (T)
Life table test	P=0.358N	P=0.091	P=0.735	P=0.741
Logistic regression test	P=0.330N	P=0.090	P=0.762	P=0.762N
Cochran-Armitage test	P=0.315N			
Fisher exact test		P=0.107	P=0.753N	P=0.753N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	6/51 (12%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.3%	15.4%	2.7%	2.8%
Terminal rate	0/41 (0%)	5/38 (13%)	1/37 (3%)	1/36 (3%)
First incidence (days)	675	718	730 (T)	730 (T)
Life table test	P=0.308N	P=0.050	P=0.735	P=0.741
Logistic regression test	P=0.281N	P=0.048	P=0.762	P=0.762N
Cochran-Armitage test	P=0.265N			
Fisher exact test		P=0.059	P=0.753N	P=0.753N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	1/51 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.6%	2.6%	2.7%	0.0%
Terminal rate	1/41 (2%)	1/38 (3%)	1/37 (3%)	0/36 (0%)
First incidence (days)	662	730 (T)	730 (T)	–
Life table test	P=0.088N	P=0.334N	P=0.352N	P=0.143N
Logistic regression test	P=0.074N	P=0.296N	P=0.302N	P=0.117N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.301N	P=0.309N	P=0.121N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/50 (8%)	1/51 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	8.7%	2.6%	2.7%	0.0%
Terminal rate	1/41 (2%)	1/38 (3%)	1/37 (3%)	0/36 (0%)
First incidence (days)	662	730 (T)	730 (T)	–
Life table test	P=0.044N	P=0.207N	P=0.224N	P=0.081N
Logistic regression test	P=0.035N	P=0.166N	P=0.172N	P=0.059N
Cochran-Armitage test	P=0.034N			
Fisher exact test		P=0.175N	P=0.181N	P=0.059N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	2/51 (4%)	4/50 (8%)	4/50 (8%)
Adjusted rate	2.4%	5.3%	10.5%	9.2%
Terminal rate	1/41 (2%)	2/38 (5%)	3/37 (8%)	0/36 (0%)
First incidence (days)	730 (T)	730 (T)	675	645
Life table test	P=0.100	P=0.473	P=0.151	P=0.164
Logistic regression test	P=0.111	P=0.473	P=0.158	P=0.185
Cochran-Armitage test	P=0.112			
Fisher exact test		P=0.508	P=0.181	P=0.181
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	2/51 (4%)	4/50 (8%)	4/50 (8%)
Adjusted rate	4.9%	5.3%	10.5%	9.2%
Terminal rate	2/41 (5%)	2/38 (5%)	3/37 (8%)	0/36 (0%)
First incidence (days)	730 (T)	730 (T)	675	645
Life table test	P=0.184	P=0.667	P=0.291	P=0.305
Logistic regression test	P=0.205	P=0.667	P=0.300	P=0.343
Cochran-Armitage test	P=0.207			
Fisher exact test		P=0.684N	P=0.339	P=0.339
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	3/51 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	7.2%	2.2%	0.0%
Terminal rate	0/41 (0%)	2/38 (5%)	0/37 (0%)	0/36 (0%)
First incidence (days)	–	484	586	–
Life table test	P=0.387N	P=0.113	P=0.483	–
Logistic regression test	P=0.363N	P=0.139	P=0.527	–
Cochran-Armitage test	P=0.368N			
Fisher exact test		P=0.125	P=0.500	–

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	6/50 (12%)	13/51 (25%)	8/50 (16%)	7/50 (14%)
Adjusted rate	13.7%	30.4%	19.1%	17.0%
Terminal rate	4/41 (10%)	9/38 (24%)	4/37 (11%)	3/36 (8%)
First incidence (days)	662	273	568	636
Life table test	P=0.512N	P=0.052	P=0.313	P=0.419
Logistic regression test	P=0.429N	P=0.074	P=0.383	P=0.488
Cochran-Armitage test	P=0.431N			
Fisher exact test		P=0.069	P=0.387	P=0.500
All Organs: Benign Neoplasms				
Overall rate	20/50 (40%)	26/51 (51%)	26/50 (52%)	16/50 (32%)
Adjusted rate	44.3%	61.8%	62.9%	39.5%
Terminal rate	16/41 (39%)	22/38 (58%)	22/37 (59%)	12/36 (33%)
First incidence (days)	662	560	521	456
Life table test	P=0.299N	P=0.101	P=0.081	P=0.433N
Logistic regression test	P=0.166N	P=0.093	P=0.115	P=0.289N
Cochran-Armitage test	P=0.152N			
Fisher exact test		P=0.182	P=0.158	P=0.266N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	27/51 (53%)	23/50 (46%)	18/50 (36%)
Adjusted rate	34.5%	53.8%	47.9%	37.5%
Terminal rate	9/41 (22%)	15/38 (39%)	12/37 (32%)	6/36 (17%)
First incidence (days)	193	273	393	456
Life table test	P=0.531N	P=0.042	P=0.117	P=0.389
Logistic regression test	P=0.250N	P=0.108	P=0.349	P=0.437N
Cochran-Armitage test	P=0.407N			
Fisher exact test		P=0.043	P=0.154	P=0.500
All Organs: Benign or Malignant Neoplasms				
Overall rate	31/50 (62%)	41/51 (80%)	38/50 (76%)	28/50 (56%)
Adjusted rate	62.0%	81.9%	77.6%	58.3%
Terminal rate	22/41 (54%)	29/38 (76%)	26/37 (70%)	16/36 (44%)
First incidence (days)	193	273	393	456
Life table test	P=0.372N	P=0.033	P=0.067	P=0.555
Logistic regression test	P=0.076N	P=0.064	P=0.118	P=0.217N
Cochran-Armitage test	P=0.129N			
Fisher exact test		P=0.034	P=0.097	P=0.342N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, ovary, pituitary gland, skin, spleen, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the 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 controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, 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 Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Overall Historical Incidence: Dermal (Acetone)			
Total	12/100 (12.0%)	6/100 (6.0%)	17/100 (17.0%)
Standard deviation	5.7%	2.8%	4.2%
Range	8%-16%	4%-8%	14%-20%
Overall Historical Incidence: Feed			
Total	176/1,462 (12.0%)	89/1,462 (6.1%)	247/1,462 (16.9%)
Standard deviation	8.2%	5.4%	10.7%
Range	0%-33%	0%-20%	3%-42%
Overall Historical Incidence: Inhalation			
Total	56/657 (8.5%)	57/657 (8.7%)	111/657 (16.9%)
Standard deviation	6.2%	4.8%	8.7%
Range	0%-22%	0%-16%	3%-31%
Overall Historical Incidence: Water Gavage			
Total	13/315 (4.1%)	8/315 (2.5%)	21/315 (6.7%)
Standard deviation	3.2%	2.1%	4.2%
Range	2%-10%	0%-6%	2%-12%
Overall Historical Incidence: Corn Oil Gavage			
Total	97/948 (10.2%)	42/948 (4.4%)	133/948 (14.0%)
Standard deviation	7.1%	3.5%	8.0%
Range	2%-26%	0%-14%	2%-34%

[a] Data as of 31 March 1993

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

	0 µL	7.5 µL	15 µL	30 µL
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	10
Early deaths				
Accidental deaths				1
Moribund	4	5	5	8
Natural deaths	5	8	7	5
Survivors				
Died last week of study		1	1	
Terminal sacrifice	41	37	36	36
Missing			1	
Animals examined microscopically	60	55	53	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(4)	(3)	(10)
Clear cell focus	1 (10%)			
Inflammation, chronic, focal	8 (80%)	4 (100%)	3 (100%)	4 (40%)
Pancreas	(10)			(10)
Edema				1 (10%)
Necrosis, focal	1 (10%)			
Endocrine System				
Adrenal cortex	(10)			(10)
Capsule, hyperplasia	10 (100%)			10 (100%)
Adrenal gland	(10)			(9)
Corticomedullary junction, degeneration	10 (100%)			9 (100%)
Parathyroid gland	(10)			(10)
Cyst				1 (10%)
Pituitary gland	(10)			(10)
Pars distalis, hyperplasia, focal	1 (10%)			2 (20%)
Thyroid gland	(10)			(10)
Infiltration cellular, lymphocyte				1 (10%)
C-cell, hyperplasia	1 (10%)			
Genital System				
Ovary	(10)			(10)
Cyst	4 (40%)			2 (20%)
Hematocyst	1 (10%)			
Uterus	(10)			(10)
Endometrium, hyperplasia, cystic	10 (100%)			10 (100%)
Hematopoietic System				
Spleen	(10)			(10)
Hematopoietic cell proliferation				1 (10%)

[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 Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
15-Month Interim Evaluation (continued)				
Nervous System				
Brain	(10)			(10)
Mineralization, focal	4 (40%)			4 (40%)
Respiratory System				
Lung	(10)			(10)
Inflammation, chronic, focal	1 (10%)			4 (40%)
Urinary System				
Kidney	(10)			(10)
Nephropathy	2 (20%)			4 (40%)
Cortex, cyst	1 (10%)			
Renal tubule, mineralization, focal				1 (10%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine small, jejunum	(48)	(44)	(50)	(48)
Hyperplasia, lymphoid			1 (2%)	
Intestine small, ileum	(47)	(44)	(49)	(47)
Abscess	1 (2%)			
Hyperplasia				1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Liver	(50)	(51)	(50)	(50)
Basophilic focus	2 (4%)	3 (6%)	6 (12%)	2 (4%)
Clear cell focus	1 (2%)		3 (6%)	1 (2%)
Clear cell focus, multiple		1 (2%)		
Cyst		1 (2%)	1 (2%)	
Eosinophilic focus	1 (2%)	4 (8%)	3 (6%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)		
Hepatodiaphragmatic nodule			1 (2%)	
Inflammation, acute, focal		1 (2%)		
Inflammation, chronic, focal	7 (14%)	9 (18%)	10 (20%)	6 (12%)
Mixed cell focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)	6 (12%)	3 (6%)	2 (4%)
Centrilobular, degeneration		1 (2%)		
Centrilobular, hypertrophy		1 (2%)		
Centrilobular, necrosis			1 (2%)	
Centrilobular, vacuolization cytoplasmic				1 (2%)
Hepatocyte, hyperplasia, focal		1 (2%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery				(3)
Fat, necrosis				2 (67%)
Pancreas	(49)	(51)	(50)	(49)
Abscess		1 (2%)		
Cyst	1 (2%)			
Cytoplasmic alteration, focal		1 (2%)	1 (2%)	
Edema			1 (2%)	
Necrosis, focal			1 (2%)	
Polyarteritis		1 (2%)		
Duct, ectasia	1 (2%)			1 (2%)
Salivary glands	(50)	(51)	(50)	(50)
Inflammation, chronic	1 (2%)			
Stomach, glandular	(50)	(51)	(50)	(50)
Erosion	1 (2%)	1 (2%)		
Ulcer		1 (2%)		
Epithelium, hyperplasia		1 (2%)		
Muscularis, mineralization		1 (2%)		
Cardiovascular System				
Heart	(50)	(51)	(50)	(50)
Cardiomyopathy	1 (2%)	1 (2%)	2 (4%)	
Thrombosis	1 (2%)			
Atrium, thrombosis				1 (2%)
Myocardium, necrosis, focal	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(51)	(50)	(50)
Accessory adrenal cortical nodule				1 (2%)
Cyst	2 (4%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		5 (10%)	3 (6%)
Hypertrophy, focal	2 (4%)	2 (4%)		
Pigmentation		1 (2%)		
Capsule, hyperplasia	47 (94%)	51 (100%)	50 (100%)	48 (96%)
Adrenal gland	(38)	(42)	(46)	(39)
Corticomedullary junction, congestion	5 (13%)	6 (14%)	3 (7%)	7 (18%)
Corticomedullary junction, degeneration	31 (82%)	39 (93%)	44 (96%)	37 (95%)
Corticomedullary junction, hemorrhage	3 (8%)	3 (7%)	7 (15%)	2 (5%)
Corticomedullary junction, pigmentation	13 (34%)	14 (33%)	8 (17%)	13 (33%)
Adrenal medulla	(50)	(51)	(50)	(50)
Hyperplasia, focal	1 (2%)			1 (2%)
Parathyroid gland	(47)	(48)	(47)	(50)
Cyst	1 (2%)		4 (9%)	
Pituitary gland	(49)	(48)	(50)	(49)
Angiectasis			1 (2%)	
Cyst	1 (2%)	2 (4%)	4 (8%)	
Pigmentation	1 (2%)			
Pars distalis, hyperplasia, focal	3 (6%)	10 (21%)	9 (18%)	7 (14%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(51)	(50)	(50)
C-cell, hyperplasia	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Follicle, cyst	1 (2%)		4 (8%)	1 (2%)
Follicle, dilatation				1 (2%)
Follicle, necrosis				1 (2%)
Follicular cell, hyperplasia	9 (18%)	12 (24%)	5 (10%)	8 (16%)
General Body System				
None				
Genital System				
Ovary	(49)	(51)	(49)	(49)
Atrophy	38 (78%)	36 (71%)	42 (86%)	37 (76%)
Congestion	1 (2%)			
Cyst	17 (35%)	23 (45%)	20 (41%)	14 (29%)
Cyst dermoid				1 (2%)
Hematocyst	6 (12%)	16 (31%)	6 (12%)	15 (31%)
Pigmentation	1 (2%)			1 (2%)
Uterus	(50)	(51)	(49)	(50)
Dilatation		3 (6%)	2 (4%)	1 (2%)
Endometrium, hyperplasia, cystic	49 (98%)	49 (96%)	47 (96%)	50 (100%)
Hematopoietic System				
Bone marrow	(50)	(51)	(50)	(50)
Sternal, myelofibrosis	45 (90%)	45 (88%)	43 (86%)	46 (92%)
Lymph node	(7)	(7)	(5)	(7)
Hyperplasia, lymphoid	1 (14%)			1 (14%)
Hemal, necrosis		1 (14%)		
Mediastinal, pigmentation				1 (14%)
Pancreatic, hyperplasia, lymphoid			1 (20%)	
Pancreatic, inflammation, chronic	1 (14%)			
Pancreatic, lymphatic, ectasia				1 (14%)
Renal, pigmentation				1 (14%)
Thoracic, hyperplasia	1 (14%)			
Lymph node, mandibular	(46)	(47)	(47)	(47)
Hyperplasia, lymphoid	1 (2%)		2 (4%)	
Inflammation, chronic	1 (2%)			
Lymph node, mesenteric	(49)	(45)	(48)	(50)
Fibrosis, focal	1 (2%)			
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	1 (2%)			
Hyperplasia, lymphoid	1 (2%)		2 (4%)	
Inflammation, chronic	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 μL	7.5 μL	15 μL	30 μL
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(51)	(50)	(50)
Hematopoietic cell proliferation	43 (86%)	44 (86%)	47 (94%)	43 (86%)
Hyperplasia, lymphoid	6 (12%)	1 (2%)	3 (6%)	3 (6%)
Hyperplasia, reticulum cell				1 (2%)
Infarct	1 (2%)			
Capsule, fibrosis	1 (2%)			
Vein, dilatation	1 (2%)			
Thymus	(41)	(40)	(35)	(45)
Hyperplasia, lymphoid			1 (3%)	
Integumentary System				
Mammary gland	(49)	(46)	(50)	(44)
Hyperplasia	1 (2%)	1 (2%)	3 (6%)	2 (5%)
Skin	(50)	(51)	(50)	(50)
Acanthosis, focal		1 (2%)		
Cyst epithelial inclusion			1 (2%)	
Edema		1 (2%)	1 (2%)	
Exudate		1 (2%)		
Control, edema			1 (2%)	
Site of application-no mass, exudate		1 (2%)		
Site of application-no mass, ulcer	1 (2%)			
Subcutaneous tissue, control, inflammation			1 (2%)	
Musculoskeletal System				
Bone	(50)	(51)	(50)	(50)
Vertebra, fracture				1 (2%)
Skeletal muscle	(1)	(1)	(1)	(4)
Hemorrhage, focal			1 (100%)	
Abdominal, pigmentation				1 (25%)
Diaphragm, pigmentation				1 (25%)
Nervous System				
Brain	(50)	(51)	(50)	(50)
Compression	1 (2%)		1 (2%)	1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Hydrocephalus		1 (2%)		
Mineralization, focal	38 (76%)	34 (67%)	36 (72%)	31 (62%)
Brain stem, hemorrhage			1 (2%)	
Spinal cord			(2)	(2)
Hemorrhage			1 (50%)	1 (50%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

	0 µL	7.5 µL	15 µL	30 µL
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(51)	(50)	(50)
Adenomatosis, focal	1 (2%)		1 (2%)	
Congestion	4 (8%)	5 (10%)	2 (4%)	2 (4%)
Hemorrhage, focal	1 (2%)		1 (2%)	1 (2%)
Hyperplasia				1 (2%)
Infarct				1 (2%)
Infiltration cellular, multifocal, lymphocyte				1 (2%)
Infiltration cellular, histiocyte			1 (2%)	
Inflammation, chronic, focal		2 (4%)	1 (2%)	
Alveolar epithelium, hyperplasia, focal			1 (2%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Peribronchial, hyperplasia, lymphoid	28 (56%)	15 (29%)	11 (22%)	15 (30%)
Nose	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Trachea	(50)	(51)	(50)	(50)
Inflammation, chronic	1 (2%)			
Special Senses System				
Eye	(1)		(1)	
Cornea, inflammation, subacute			1 (100%)	
Cornea, necrosis	1 (100%)			
Urinary System				
Kidney	(50)	(51)	(50)	(50)
Metaplasia, focal, osseous		1 (2%)		1 (2%)
Metaplasia, osseous	2 (4%)			
Nephropathy	7 (14%)	18 (35%)	15 (30%)	6 (12%)
Capsule, inflammation, focal		1 (2%)		
Cortex, atrophy, focal	2 (4%)	4 (8%)	3 (6%)	3 (6%)
Cortex, cyst		1 (2%)		
Cortex, metaplasia, focal, osseous		1 (2%)		
Pelvis, crystals	1 (2%)			
Pelvis, dilatation	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Proximal convoluted renal tubule, cytoplasmic alteration		2 (4%)	1 (2%)	
Renal tubule, mineralization, focal	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Urinary bladder	(49)	(47)	(49)	(48)
Infiltration cellular, focal, lymphocyte				1 (2%)
Inflammation, chronic				1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL 228
CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS 228
RESULTS 229
TABLE E1 Mutagenicity of Dimethylphthalate in ***Salmonella typhimurium*** 231
TABLE E2 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Dimethylphthalate 233
TABLE E3 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Dimethylphthalate 235
TABLE E4 Mutagenicity of Diethylphthalate in ***Salmonella typhimurium*** 236
TABLE E5 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Diethylphthalate 238
TABLE E6 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Diethylphthalate 240

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1985). Dimethylphthalate and diethylphthalate were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). They were incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of dimethylphthalate or diethylphthalate. The high dose of dimethylphthalate was limited by toxicity; the high dose of diethylphthalate was 10,000 μg/plate. All trials were repeated.

In this test, 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 which is not dose-related, 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. No minimum percentage or fold increase is required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987) and by Loveday *et al.* (1990). Dimethylphthalate and diethylphthalate were sent to the laboratories as coded aliquots by Radian Corporation. They were 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 dimethylphthalate or diethylphthalate. The high dose of dimethylphthalate was 5,100 μg/mL; the high dose of diethylphthalate was 750 μg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with dimethylphthalate or diethylphthalate in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing dimethylphthalate or diethylphthalate was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 to 3 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 dimethylphthalate or diethylphthalate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no dimethylphthalate or diethylphthalate, and incubation proceeded for an additional 26 to 27 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. Because significant chemical-induced cell cycle delay was seen with diethylphthalate, incubation time was lengthened for the 750 μg/mL dose to ensure a sufficient number of scorable (second-division metaphase) cells.

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 ($P \leq 0.05$) 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 dimethylphthalate for 8.5 hours or diethylphthalate for 13.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with dimethylphthalate or diethylphthalate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for approximately 10 hours in fresh medium, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. The harvest time for the Abs test with dimethylphthalate was based on the cell cycle information obtained in the SCE test: because some cell cycle delay was anticipated, the incubation period for the second trial with S9 was extended from the normal period of 12 to 14 hours.

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. For the SCE test, 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 200 first-division metaphase cells were scored at each dose level for the Abs test. 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. Statistical analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive (Galloway *et al.*, 1987).

RESULTS

Dimethylphthalate: Dimethylphthalate (33 to 6,666 μg/plate) did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Zeiger *et al.*, 1985).

In cytogenetic tests with cultured Chinese hamster ovary cells, dimethylphthalate induced sister chromatid exchanges in the presence, but not the absence, of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E2; Loveday *et al.*, 1990). Except for the positive response noted at 151 μg/mL in the first trial with S9, concentrations above 1,000 μg/mL were necessary to induce an increase in SCEs. The increases in SCEs observed after treatment with dimethylphthalate, although small, were well-correlated with dose. Dimethylphthalate was less toxic to CHO cells than was diethylphthalate in these studies.

No induction of chromosomal aberrations was observed in CHO cells treated with dimethylphthalate with or without S9 (Table E3; Loveday *et al.*, 1990). Two trials were conducted with S9, one using the standard 12 hour incubation period and the second using an extended incubation time of 20.5 hours to ensure that

harvested CHO cells were exposed to dimethylphthalate for at least one complete cell cycle. No significant increase in Abs was noted in either trial, where the highest dose tested was 5,100 μg/mL.

Diethylphthalate: Diethylphthalate (10 to 10,000 μg/plate) was tested by two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, (Table E4; Zeiger *et al.*, 1985). Testing was performed using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. High dose was limited by toxicity to 3,333 μg/plate in the first laboratory, but reached the maximum concentration (10,000 μg/plate) permitted by the testing protocol in the second laboratory. Negative results were obtained with diethylphthalate at both laboratories in all four tester strains.

In cytogenetic tests with cultured Chinese hamster ovary cells, diethylphthalate induced sister chromatid exchanges in the presence of Aroclor 1254-induced rat liver S9 (Table E5) but not chromosomal aberrations, with or without S9 (Table E6). Significant increases in SCEs were obtained at concentrations of 167 to 750 μg/mL diethylphthalate; cell cycle delay, indicative of chemical-related toxicity, was observed only at the 750 μg/mL level. The small dose-related increase in chromosomal aberrations observed in the one trial without S9 was insufficient for a positive call because no single dose was significantly elevated above the control, and the trend test P value was not less than 0.003.

In conclusion, neither dimethylphthalate nor diethylphthalate induced mutations in *Salmonella* or chromosomal aberrations in CHO cells. However, both chemicals induced SCEs in CHO cells in the presence of S9. A comparative evaluation of *in vitro* genetic toxicity and rodent bioassay test results by the NTP showed that, although the positive SCE test might indicate a potential for *in vivo* DNA damage, this endpoint is highly sensitive and does not correlate well with carcinogenic effects in rodents (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). Only 64% of chemicals which induced SCEs *in vitro* were also carcinogenic in rats and/or mice. Thus, positive results in the SCE test have a low positive predictivity for carcinogenicity in rodents. The negative results obtained in the other *in vitro* genetic toxicity tests with dimethylphthalate and diethylphthalate do not further aid in classifying the chemicals as to their activity in the rodent bioassay. In the NTP evaluation of *in vitro* genetic toxicity tests, only about 50% of the nonmutagens were also found to be noncarcinogens.

TABLE E1
Mutagenicity of Dimethylphthalate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	111 ± 6.0	156 ± 4.5	141 ± 12.7	144 ± 8.6	135 ± 9.7	131 ± 4.7
	33	117 ± 8.1	147 ± 10.8				
	100	116 ± 9.8	146 ± 12.3	142 ± 11.9	134 ± 6.4	125 ± 10.8	145 ± 8.5
	333	134 ± 2.6	146 ± 4.2	137 ± 14.5	126 ± 9.4	120 ± 8.7	120 ± 3.8
	1,000	131 ± 6.1	148 ± 7.5	131 ± 12.5	136 ± 2.3	122 ± 9.1	118 ± 6.8
	2,166	124 ± 5.0					
	3,000		149 ± 10.4[c]				
	3,333			140 ± 6.0	114 ± 11.8[c]	114 ± 6.3	99 ± 3.2[c]
	5,000				98 ± 10.7[c]		90 ± 8.0[c]
	6,666			Toxic		86 ± 0.5[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,066 ± 8.1	1,484 ± 57.2	1,096 ± 36.8	1,535 ± 35.7	698 ± 12.9	983 ± 96.5
TA1535	0	21 ± 2.6	28 ± 0.7	12 ± 1.7	10 ± 2.7	14 ± 0.7	12 ± 0.9
	33	27 ± 4.1	26 ± 3.2				
	100	25 ± 2.7	23 ± 3.4	11 ± 1.5	7 ± 1.5	12 ± 0.9	10 ± 1.7
	333	17 ± 1.7	29 ± 1.2	10 ± 1.5	13 ± 1.9	12 ± 1.5	13 ± 1.5
	1,000	25 ± 5.5	34 ± 3.9	16 ± 2.3	11 ± 1.7	12 ± 0.7	12 ± 1.2
	2,166	26 ± 2.9					
	3,000		32 ± 1.9[c]				
	3,333			9 ± 0.0	8 ± 1.0[c]	12 ± 3.2	11 ± 3.8
	5,000				Toxic		9 ± 1.7[c]
	6,666			Toxic		10 ± 1.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		853 ± 17.0	1,057 ± 7.5	75 ± 9.3	88 ± 5.3	59 ± 6.7	68 ± 2.7
TA1537	0	5 ± 0.9	5 ± 1.2	8 ± 0.7	8 ± 2.1	6 ± 0.0	7 ± 0.9
	33	5 ± 2.0	5 ± 1.3				
	100	11 ± 2.0	6 ± 1.0	6 ± 0.3	5 ± 0.3	9 ± 0.7	9 ± 1.2
	333	5 ± 1.2	10 ± 1.5	8 ± 0.9	10 ± 0.3	8 ± 0.3	8 ± 0.7
	1,000	6 ± 1.5	6 ± 0.6	5 ± 0.9	7 ± 0.7	6 ± 1.8	7 ± 1.2
	2,166	7 ± 1.3					
	3,000		4 ± 1.5[c]				
	3,333			7 ± 1.5	4 ± 1.7[c]	6 ± 1.3	6 ± 1.7[c]
	5,000				5 ± 0.7[c]		Toxic
	6,666			3 ± 0.7[c]		6 ± 2.3[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		623 ± 104.6	225 ± 23.2	92 ± 5.2	120 ± 9.4	46 ± 5.9	67 ± 5.9

TABLE E1
Mutagenicity of Dimethylphthalate in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98	0	19 ± 0.9	16 ± 2.2	27 ± 5.3	26 ± 2.0	22 ± 1.3	30 ± 2.0
	33	17 ± 2.9	19 ± 3.5				
	100	18 ± 1.9	18 ± 4.4	28 ± 2.3	31 ± 0.3	21 ± 2.5	27 ± 1.0
	333	14 ± 1.9	17 ± 2.5	25 ± 3.1	26 ± 1.2	23 ± 4.8	23 ± 1.5
	1,000	16 ± 1.2	19 ± 1.5	32 ± 4.4	27 ± 2.2	20 ± 4.6	25 ± 3.9
	2,166	14 ± 1.0					
	3,000		19 ± 1.7				
	3,333			23 ± 5.0	28 ± 2.7	18 ± 2.0	19 ± 2.3[c]
	5,000				18 ± 3.8[c]		15 ± 3.5[c]
	6,666			14 ± 2.6[c]		15 ± 1.2[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,282 ± 67.1	1,245 ± 60.7	848 ± 14.1	1,366 ± 32.3	415 ± 16.3	747 ± 20.9

[a] High dose was limited by toxicity. The detailed protocol and these data are presented in Zeiger *et al.* (1985). Study conducted at EG&G Mason Research Institute.
[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 (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Dimethylphthalate[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide		50	1,025	372	0.36	7.4	26.5	
Mitomycin-C	0.002	50	1,036	585	0.56	11.7	26.5	55.59
	0.010	10	208	222	1.06	22.2	26.5	194.09
Dimethylphthalate	50	50	1,037	369	0.35	7.4	26.5	−1.95
	151	50	1,030	388	0.37	7.8	26.5	3.79
	500	50	1,039	407	0.39	8.1	26.5	7.94
					P=0.103[c]			
+S9								
Trial 1								
Summary: Equivocal								
Dimethylsulfoxide		50	1,039	437	0.42	8.7	26.0	
Cyclophosphamide	0.5	50	1,047	605	0.57	12.1	26.0	37.39
	2.5	10	210	285	1.35	28.5	26.0	222.68
Dimethylphthalate	151	50	1,045	528	0.50	10.6	26.0	20.13*
	500	50	1,040	465	0.44	9.3	26.0	6.31
	1,510	50	1,045	413	0.39	8.3	26.0	−6.04
					P=0.927			

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Dimethylphthalate (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9 (continued)								
Trial 2								
Summary: Weak positive								
Dimethylsulfoxide		50	1,047	424	0.40	8.5	26.0	
Cyclophosphamide	0.5	50	1,046	1,008	0.96	20.2	26.0	137.97
	2.5	10	209	589	2.81	58.9	26.0	595.92
Dimethylphthalate	248	50	1,036	410	0.39	8.2	26.0	−2.28
	414	50	1,047	478	0.45	9.6	26.0	12.74
	1,240	50	1,050	530	0.50	10.6	26.0	24.64*
					P<0.001			
Trial 3								
Summary: Positive								
Dimethylsulfoxide		50	1,048	428	0.40	8.6	26.0	
Cyclophosphamide	0.4	50	1,051	674	0.64	13.5	26.0	57.03
	2.5	10	210	382	1.81	38.2	26.0	345.42
Dimethylphthalate	494	50	1,050	402	0.38	8.0	26.0	−6.25
	988	50	1,045	503	0.48	10.1	26.0	17.86
	1,980	50	1,047	540	0.51	10.8	26.0	26.29*
	2,960	50	1,042	562	0.53	11.2	26.0	32.06*
					P<0.001			

* Positive response (≥20% increase over solvent control)
[a] Study performed at Bioassay Systems Corporation. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol and these data are presented by Loveday *et al.* (1990).
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Dimethylphthalate[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 10.5 hours Summary: Negative					**Trial 1** - Harvest time: 12.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	3	0.02	1.5		200	11	0.06	5.0
Mitomycin-C					Cyclophosphamide				
0.75	200	30	0.15	10.5	50	50	57	1.14	46.0
5.00	50	18	0.36	26.0					
Dimethylphthalate					Dimethylphthalate				
150	200	5	0.03	1.0	498	200	11	0.06	5.5
498	200	2	0.01	1.0	1,500	200	14	0.07	6.5
1,500	200	0	0.00	0.0	4,980	200	21	0.11	8.5
				P=0.935[b]					P=0.068
					Trial 2 - Harvest time: 20.5 hours[c] Summary: Negative				
					Dimethylsulfoxide				
						200	5	0.03	2.0
					Cyclophosphamide				
					50	10	87	8.70	100.0
					Dimethylphthalate				
					3,060	200	7	0.04	3.0
					4,080	200	33	0.17	2.5
					5,100	200	19	0.10	5.5
									P=0.042

[a] Study performed at Bioassay Systems Corporation. Abs = aberrations. A detailed presentation of the protocol and these data are found in Loveday *et al.* (1990).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.
[c] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.

TABLE E4
Mutagenicity of Diethylphthalate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study conducted at EG&G Mason Research Institute							
TA100	0	105 ± 1.2	114 ± 3.3	116 ± 4.4	105 ± 7.2	113 ± 9.9	129 ± 6.0
	10	100 ± 10.4	130 ± 5.9		108 ± 8.4		127 ± 1.2
	33	106 ± 9.7	127 ± 5.3	114 ± 5.3	114 ± 8.6	114 ± 10.9	126 ± 4.6
	100	123 ± 3.8	126 ± 1.2	102 ± 11.6	126 ± 6.7	104 ± 1.5	130 ± 5.0
	333	115 ± 7.5	128 ± 0.9	87 ± 4.7	117 ± 4.9	117 ± 5.8	130 ± 1.7
	667		144 ± 5.8[c]				
	1,000	Toxic		102 ± 8.0[c]	98 ± 3.0[c]	117 ± 5.2[c]	136 ± 4.7[c]
	3,333			Toxic		Toxic	
Trial summary		Negative	Equivocal	Negative	Negative	Negative	Negative
Positive control[d]		1,356 ± 8.4	1,463 ± 26.3	1,230 ± 70.8	2,668 ± 64.9	1,092 ± 42.8	1,416 ± 7.7
TA1535	0	20 ± 2.7	49 ± 3.3	11 ± 2.8	14 ± 3.0	11 ± 0.7	12 ± 0.3
	10	23 ± 1.5	43 ± 3.8		12 ± 1.0		12 ± 0.9
	33	24 ± 3.9	46 ± 2.6	10 ± 0.3	14 ± 3.7	9 ± 0.6	10 ± 1.5
	100	23 ± 2.2	49 ± 0.3	11 ± 1.7	14 ± 3.8	10 ± 2.4	18 ± 2.1
	333	21 ± 2.7	49 ± 7.0	11 ± 0.9	11 ± 0.0	11 ± 0.9	20 ± 0.6
	667		47 ± 0.7[c]				
	1,000	Toxic		8 ± 1.0[c]	10 ± 2.2[c]	10 ± 3.1[c]	13 ± 1.2[c]
	3,333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,127 ± 38.8	2,216 ± 19.6	116 ± 7.9	251 ± 0.6	99 ± 12.4	61 ± 5.4
TA1537	0	8 ± 0.9	5 ± 1.7	7 ± 0.9	9 ± 1.9	6 ± 0.9	7 ± 1.9
	10	4 ± 0.3	7 ± 0.7		10 ± 1.8		11 ± 1.8
	33	7 ± 1.8	5 ± 1.2	12 ± 0.9	9 ± 1.0	11 ± 1.5	9 ± 0.3
	100	8 ± 0.5	5 ± 1.0	9 ± 1.2	5 ± 0.3	10 ± 2.3	10 ± 1.5
	333	6 ± 1.2	7 ± 2.6	9 ± 2.4	10 ± 0.9	8 ± 1.2	6 ± 2.7
	667		6 ± 1.2[c]				
	1,000	Toxic		6 ± 1.9[c]	10 ± 3.5[c]	7 ± 0.6	7 ± 1.3[c]
	3,333			5 ± 0.0[c]		5 ± 1.2[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		301 ± 102.6	161 ± 19.7	111 ± 7.2	206 ± 16.5	119 ± 11.0	137 ± 4.0
TA98	0	21 ± 5.6	18 ± 2.4	27 ± 1.5	30 ± 1.5	26 ± 2.0	38 ± 0.7
	10	16 ± 3.0	22 ± 0.9		29 ± 0.7		34 ± 4.3
	33	22 ± 1.0	17 ± 0.9	30 ± 1.7	28 ± 5.5	34 ± 1.2	33 ± 4.4
	100	23 ± 0.6	23 ± 1.7	26 ± 2.0	29 ± 2.6	29 ± 5.4	28 ± 2.1
	333	15 ± 0.3	20 ± 1.7	26 ± 2.3	27 ± 2.0	29 ± 3.9	29 ± 6.2
	667		16 ± 3.7				
	1,000	Toxic		22 ± 5.1[c]	27 ± 2.3[c]	30 ± 3.2[c]	30 ± 0.3
	3,333			27 ± 2.3[c]		12 ± 1.5[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,492 ± 27.5	1,548 ± 23.9	1,252 ± 62.4	2,265 ± 15.9	1,119 ± 59.7	994 ± 61.7

TABLE E4
Mutagenicity of Diethylphthalate in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study conducted at Case Western Reserve University							
TA100	0	105 ± 6.7	106 ± 2.9	132 ± 9.2	155 ± 11.6	138 ± 7.5	178 ± 33.8
	100	99 ± 6.1	118 ± 7.3	137 ± 5.2	171 ± 5.2	151 ± 4.3	174 ± 12.2
	333	103 ± 13.3	123 ± 10.8	132 ± 2.9	160 ± 4.5	141 ± 8.3	193 ± 18.7
	1,000	81 ± 2.4	90 ± 11.0	127 ± 18.1	164 ± 8.1	140 ± 2.6	170 ± 6.5
	3,333	90 ± 4.4	105 ± 5.2	133 ± 2.9	189 ± 16.8	139 ± 4.5	174 ± 9.2
	10,000	67 ± 3.5	83 ± 5.0	132 ± 6.0	151 ± 3.0	161 ± 3.5	172 ± 8.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		659 ± 23.0	566 ± 22.8	2,281 ± 69.4	3,024 ± 210.7	1,044 ± 14.7	1,684 ± 89.9
TA1535	0	4 ± 1.2	4 ± 0.9	4 ± 0.9	5 ± 0.3	5 ± 0.7	6 ± 0.7
	100	5 ± 1.0	5 ± 1.5	4 ± 0.3	5 ± 0.6	3 ± 0.6	3 ± 0.9
	333	3 ± 0.3	4 ± 0.6	4 ± 0.9	5 ± 0.9	5 ± 0.0	5 ± 0.7
	1,000	2 ± 0.3	4 ± 1.2	3 ± 0.7	6 ± 1.2	2 ± 0.6	6 ± 2.0
	3,333	2 ± 0.3	3 ± 1.0	1 ± 0.0	3 ± 0.9	4 ± 0.9	7 ± 1.2
	10,000	1 ± 0.3	2 ± 0.6	2 ± 0.0	3 ± 0.6	4 ± 0.6	4 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		296 ± 6.6	609 ± 19.2	79 ± 2.7	91 ± 8.4	28 ± 5.7	66 ± 8.8
TA1537	0	10 ± 4.7	7 ± 1.7	10 ± 0.7	12 ± 1.7	18 ± 3.1	9 ± 1.8
	100	8 ± 0.6	3 ± 1.5	6 ± 0.3	5 ± 1.5	16 ± 0.9	9 ± 1.0
	333	9 ± 0.9	6 ± 0.3	5 ± 0.0	8 ± 1.2	13 ± 1.0	6 ± 0.6
	1,000	7 ± 0.7	3 ± 1.2	7 ± 0.0	7 ± 0.7	14 ± 0.9	7 ± 2.6
	3,333	4 ± 2.0	3 ± 0.9	6 ± 0.9	8 ± 1.0	11 ± 2.1	8 ± 1.7
	10,000	5 ± 0.3	2 ± 1.2	5 ± 1.5	5 ± 0.3	10 ± 0.7	6 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		788 ± 169.0	1,206 ± 432.4	675 ± 15.3	284 ± 16.5	121 ± 4.1	49 ± 5.5
TA98	0	17 ± 4.1	17 ± 2.0	21 ± 3.8	25 ± 6.7	21 ± 0.0	23 ± 2.7
	100	19 ± 3.8	13 ± 3.0	27 ± 1.8	27 ± 3.2	26 ± 2.0	26 ± 1.5
	333	19 ± 3.8	18 ± 0.7	26 ± 1.0	24 ± 6.4	22 ± 2.6	17 ± 4.1
	1,000	18 ± 3.4	13 ± 3.5	29 ± 3.8	22 ± 6.7	25 ± 1.5	25 ± 1.2
	3,333	17 ± 0.3	16 ± 1.5	17 ± 1.5	20 ± 2.6	21 ± 1.2	19 ± 2.1
	10,000	21 ± 3.5	18 ± 2.2	24 ± 0.7	19 ± 5.0	19 ± 1.5	18 ± 1.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		430 ± 13.0	369 ± 9.0	1,725 ± 61.8	2,390 ± 167.8	844 ± 78.7	577 ± 25.6

[a] The detailed protocol and these data are presented in Zeiger *et al.* (1985).
[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 (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E5
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Diethylphthalate[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide		50	1,044	392	0.37	7.8	26.0	
Mitomycin-C	0.001	50	1,046	549	0.52	11.0	26.0	39.78
	0.004	10	210	182	0.86	18.2	26.0	130.82
Diethylphthalate	5	50	1,045	417	0.39	8.3	26.0	6.28
	17	50	1,043	436	0.41	8.7	26.0	11.33
	50	50	1,045	377	0.36	7.5	26.0	−3.92
					P=0.598[c]			
+S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,047	359	0.34	7.2	26.0	
Cyclophosphamide	0.125	50	1,048	675	0.64	13.5	26.0	87.84
	0.500	10	208	204	0.98	20.4	26.0	186.04
Diethylphthalate	50	50	1,044	412	0.39	8.2	26.0	15.09
	167	50	1,045	465	0.44	9.3	26.0	29.77*
	500	50	1,043	588	0.56	11.8	26.0	64.42*
					P<0.001			

TABLE E5
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Diethylphthalate (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9 (continued)								
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,048	395	0.38	7.9	26.0	
		50	1,050	445	0.42	8.9	31.0[d]	
Cyclophosphamide	0.125	50	1,048	650	0.62	13.0	26.0	46.35
	0.500	10	211	213	1.00	21.3	26.0	138.19
Diethylphthalate	167	50	1,053	513	0.48	10.3	26.0	14.95
	500	50	1,049	561	0.53	11.2	26.0	26.19*
	750	50	1,047	710	0.67	14.2	31.0[d]	60.01*
					P<0.001			

* Positive response (≥20% increase over solvent control)
[a] Study performed at Sitek Research Laboratories. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987).
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.
[d] Because of chemical-induced delay in the cell-division cycle, harvest time was extended to maximize the proportion of second-division metaphase cells available for analysis.

TABLE E6
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Diethylphthalate[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 15.5 hours Summary: Negative					Harvest time: 12.5 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	3	0.02	1.5
Mitomycin-C					Cyclophosphamide				
0.4	25	13	0.52	36.0	20	25	15	0.60	40.0
Diethylphthalate					Diethylphthalate				
70	200	0	0.00	0.0	70	200	2	0.01	1.0
151	200	1	0.01	0.5	151	200	2	0.01	1.0
324	200	5	0.03	2.5	324	200	1	0.01	0.5
				P=0.014[b]					P=0.830

[a] Study performed at Sitek Research Laboratories. Abs = aberrations. A detailed presentation of the protocol is found in Galloway *et al.* (1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

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

TABLE F1	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 4-Week Dermal Study of Diethylphthalate	242
TABLE F2	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate	243
TABLE F3	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 4-Week Dermal Study of Diethylphthalate	244
TABLE F4	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate	245

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 4-Week Dermal Study of Diethylphthalate[a]

	0 μL	37.5 μL	75 μL	150 μL	300 μL
Male					
n	10	10	10	10	10
Necropsy body wt	235 ± 5	229 ± 7	226 ± 9	222 ± 4	220 ± 5
R. Kidney					
Absolute	1.146 ± 0.035	1.107 ± 0.035	1.085 ± 0.028	1.189 ± 0.028	1.165 ± 0.023
Relative	4.87 ± 0.11	4.84 ± 0.06	4.85 ± 0.20	5.35 ± 0.07*	5.29 ± 0.09*
Liver					
Absolute	12.103 ± 0.408	11.982 ± 0.479	12.063 ± 0.651	12.137 ± 0.276	12.549 ± 0.351
Relative	51.41 ± 1.10	52.35 ± 1.24	52.99 ± 1.42	54.64 ± 1.00	56.92 ± 0.85**
R. Testis					
Absolute	1.377 ± 0.016	1.335 ± 0.029	1.343 ± 0.024	1.343 ± 0.016	1.353 ± 0.021
Relative	5.87 ± 0.08	5.86 ± 0.10	6.02 ± 0.26	6.05 ± 0.07	6.15 ± 0.07
Thymus					
Absolute	0.423 ± 0.021	0.399 ± 0.016	0.389 ± 0.013	0.384 ± 0.015	0.393 ± 0.011
Relative	1.80 ± 0.09	1.76 ± 0.11	1.73 ± 0.04	1.73 ± 0.07	1.79 ± 0.05
Female					
n	10	10	10	10	10
Necropsy body wt	144 ± 2	142 ± 3	145 ± 3	141 ± 2	138 ± 3
R. Kidney					
Absolute	0.755 ± 0.020	0.732 ± 0.019	0.791 ± 0.011	0.801 ± 0.023	0.753 ± 0.017
Relative	5.26 ± 0.13	5.16 ± 0.10	5.46 ± 0.08	5.69 ± 0.11*	5.46 ± 0.09
Liver					
Absolute	6.422 ± 0.167	6.566 ± 0.201	6.823 ± 0.225	6.810 ± 0.143	6.578 ± 0.139
Relative	44.65 ± 0.80	46.28 ± 1.10	46.92 ± 1.05	48.41 ± 0.85*	47.69 ± 0.55*
Thymus					
Absolute	0.317 ± 0.009	0.323 ± 0.012	0.306 ± 0.015	0.308 ± 0.014	0.312 ± 0.011
Relative	2.21 ± 0.08	2.29 ± 0.10	2.10 ± 0.07	2.19 ± 0.09	2.27 ± 0.10

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

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate[a]

	0 μL	100 μL	300 μL
Male			
n	10	10	9
Necropsy body wt	436 ± 11	419 ± 18	406 ± 9
Brain			
Absolute	2.048 ± 0.020	1.987 ± 0.044	1.936 ± 0.022*
Relative	4.72 ± 0.12	4.84 ± 0.28	4.78 ± 0.09
R. Kidney			
Absolute	1.666 ± 0.054	1.700 ± 0.061	1.687 ± 0.050
Relative	3.83 ± 0.13	4.13 ± 0.25	4.17 ± 0.15
Liver			
Absolute	15.139 ± 0.643	15.491 ± 0.670	15.026 ± 0.450
Relative	34.69 ± 1.14	37.72 ± 2.59	37.07 ± 1.08
Female			
n	8	10	10
Necropsy body wt	268 ± 6	261 ± 8	263 ± 9
Brain			
Absolute	1.873 ± 0.019	1.839 ± 0.029	1.875 ± 0.017
Relative	7.00 ± 0.15	7.11 ± 0.24	7.20 ± 0.24
R. Kidney			
Absolute	1.074 ± 0.027	1.079 ± 0.035	1.109 ± 0.028
Relative	4.02 ± 0.12	4.17 ± 0.17	4.25 ± 0.14
Liver			
Absolute	9.573 ± 0.175	9.699 ± 0.317	9.728 ± 0.279
Relative	35.78 ± 0.83	37.48 ± 1.53	37.20 ± 1.06

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 4-Week Dermal Study of Diethylphthalate[a]

	0 μL	12.5 μL	25 μL	50 μL	100 μL
Male					
n	10	10	10	10	10
Necropsy body wt	26.8 ± 0.6	27.1 ± 0.6	26.1 ± 0.5	26.8 ± 0.4	26.5 ± 0.6
R. Kidney					
Absolute	0.334 ± 0.007	0.310 ± 0.013	0.313 ± 0.010	0.344 ± 0.014	0.340 ± 0.014
Relative	12.50 ± 0.33	11.45 ± 0.40	11.98 ± 0.31	12.81 ± 0.42	12.81 ± 0.34
Liver					
Absolute	1.683 ± 0.053	1.746 ± 0.060	1.702 ± 0.048	1.721 ± 0.025	1.716 ± 0.056
Relative	62.78 ± 1.07	64.34 ± 1.12	65.04 ± 0.86	64.37 ± 0.72	64.76 ± 1.06
R. Testis					
Absolute	0.118 ± 0.003	0.114 ± 0.004	0.115 ± 0.004	0.118 ± 0.003	0.116 ± 0.003
Relative	4.44 ± 0.20	4.21 ± 0.18	4.41 ± 0.16	4.40 ± 0.12	4.38 ± 0.13
Thymus					
Absolute	0.054 ± 0.003	0.055 ± 0.002	0.052 ± 0.003	0.053 ± 0.003	0.055 ± 0.003
Relative	2.02 ± 0.14	2.05 ± 0.08	1.99 ± 0.14	1.98 ± 0.14	2.06 ± 0.12
Female					
n	9	10	10	10	10
Necropsy body wt	21.9 ± 0.5	22.4 ± 0.4	23.1 ± 0.3	22.5 ± 0.3	22.7 ± 0.3
R. Kidney					
Absolute	0.231 ± 0.011	0.231 ± 0.006	0.247 ± 0.008	0.230 ± 0.007	0.229 ± 0.007
Relative	10.60 ± 0.51	10.35 ± 0.25	10.71 ± 0.32	10.24 ± 0.29	10.07 ± 0.23
Liver					
Absolute	1.365 ± 0.056	1.493 ± 0.038	1.569 ± 0.037*	1.491 ± 0.057	1.562 ± 0.037*
Relative	62.30 ± 1.48	66.76 ± 1.12	67.93 ± 1.00*	66.27 ± 1.62	68.77 ± 1.09**
Thymus					
Absolute	0.072 ± 0.004	0.074 ± 0.004	0.084 ± 0.006	0.071 ± 0.005	0.074 ± 0.004
Relative	3.29 ± 0.20	3.29 ± 0.16	3.67 ± 0.29	3.16 ± 0.23	3.25 ± 0.16

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate[a]

	0 μL	7.5 μL	15 μL	30 μL
Male				
n	10	10	10	10
Necropsy body wt	39.9 ± 0.9	37.6 ± 0.9	40.8 ± 0.6	37.8 ± 0.9
Brain				
Absolute	0.468 ± 0.005	0.456 ± 0.004	0.462 ± 0.003	0.456 ± 0.004
Relative	11.79 ± 0.27	12.20 ± 0.33	11.34 ± 0.13	12.12 ± 0.34
R. Kidney				
Absolute	0.410 ± 0.009	0.402 ± 0.008	0.390 ± 0.011	0.373 ± 0.007**
Relative	10.30 ± 0.12	10.73 ± 0.24	9.56 ± 0.22	9.89 ± 0.20
Liver				
Absolute	1.752 ± 0.070	1.709 ± 0.051	1.771 ± 0.078	1.748 ± 0.142
Relative	44.00 ± 1.60	45.50 ± 0.97	43.40 ± 1.71	46.29 ± 3.80
Female				
n	10	9	10	10
Necropsy body wt	39.1 ± 0.5	36.5 ± 1.1	37.5 ± 0.8	36.0 ± 0.9*
Brain				
Absolute	0.473 ± 0.004	0.473 ± 0.003	0.478 ± 0.005	0.472 ± 0.006
Relative	12.11 ± 0.18	13.06 ± 0.33	12.80 ± 0.35	13.16 ± 0.33*
R. Kidney				
Absolute	0.273 ± 0.004	0.271 ± 0.009	0.286 ± 0.005	0.272 ± 0.011
Relative	7.00 ± 0.16	7.44 ± 0.15	7.64 ± 0.15*	7.55 ± 0.22*
Liver				
Absolute	1.623 ± 0.051	1.500 ± 0.060	1.551 ± 0.039	1.536 ± 0.030[b]
Relative	41.49 ± 1.13	41.22 ± 1.50	41.47 ± 1.25	43.31 ± 0.80[b]

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1 Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate 248

TABLE G2 Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate 249

TABLE G1
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate[a]

	0 μL	100 μL	300 μL
Male			
n	10	10	9
Hematology			
Hematocrit (%)	41.0 ± 1.7	39.1 ± 1.1	38.3 ± 1.5
Hemoglobin (g/dL)	16.1 ± 0.6	15.6 ± 0.4	15.6 ± 0.3
Erythrocytes (10^6/μL)	8.00 ± 0.33	7.38 ± 0.30	7.49 ± 0.28
Mean cell volume (fL)	51.2 ± 0.2	53.3 ± 1.1	51.1 ± 0.3
Mean cell hemoglobin (pg)	20.2 ± 0.2	21.3 ± 0.6	21.1 ± 1.1
Mean cell hemoglobin concentration (g/dL)	39.4 ± 0.4	40.0 ± 0.4	41.3 ± 2.3
Leukocytes (10^3/μL)	8.82 ± 0.71	7.85 ± 0.66	8.20 ± 0.45
Segmented neutrophils (10^3/μL)	2.50 ± 0.18	2.57 ± 0.33	2.69 ± 0.18
Lymphocytes (10^3/μL)	6.08 ± 0.60	5.07 ± 0.36	5.32 ± 0.30
Monocytes (10^3/μL)	0.03 ± 0.02	0.05 ± 0.02	0.04 ± 0.02
Eosinophils (10^3/μL)	0.16 ± 0.05	0.17 ± 0.04	0.13 ± 0.04
Nucleated erythrocytes (10^3/μL)	0.07 ± 0.03	0.08 ± 0.03	0.10 ± 0.05
Clinical Chemistry			
Urea nitrogen (mg/dL)	22.0 ± 1.1	23.2 ± 1.4	22.7 ± 0.9
Creatinine (mg/dL)	0.56 ± 0.03	0.60 ± 0.03	0.53 ± 0.04
Alkaline phosphatase (IU/L)	238 ± 12	231 ± 15	255 ± 10
Sorbitol dehydrogenase (IU/L)	19 ± 1	19 ± 1	19 ± 1
Female			
n	8	10	10
Hematology			
Hematocrit (%)	40.7 ± 0.4	41.2 ± 0.7	43.2 ± 1.0*
Hemoglobin (g/dL)	15.3 ± 0.2	15.6 ± 0.3	16.4 ± 0.4*
Erythrocytes (10^6/μL)	7.59 ± 0.10	7.74 ± 0.12	7.99 ± 0.20*
Mean cell volume (fL)	53.6 ± 0.2	53.2 ± 0.4	54.0 ± 0.2
Mean cell hemoglobin (pg)	20.2 ± 0.1	20.1 ± 0.2	20.5 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.8 ± 0.3	37.9 ± 0.2	38.1 ± 0.3
Leukocytes (10^3/μL)	5.45 ± 0.26	5.25 ± 0.26	5.95 ± 0.26
Segmented neutrophils (10^3/μL)	1.64 ± 0.19	1.64 ± 0.25	1.73 ± 0.11
Lymphocytes (10^3/μL)	3.70 ± 0.17	3.50 ± 0.17	4.11 ± 0.17
Monocytes (10^3/μL)	0.04 ± 0.02	0.01 ± 0.01	0.04 ± 0.02
Eosinophils (10^3/μL)	0.09 ± 0.02	0.10 ± 0.03	0.08 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.07 ± 0.04	0.08 ± 0.03	0.07 ± 0.03
Clinical Chemistry			
Urea nitrogen (mg/dL)	22.5 ± 1.1	23.0 ± 0.5	22.6 ± 1.0
Creatinine (mg/dL)	0.55 ± 0.03	0.56 ± 0.03	0.51 ± 0.02
Alkaline phosphatase (IU/L)	213 ± 8	237 ± 11	247 ± 12*
Sorbitol dehydrogenase (IU/L)	21 ± 0	19 ± 1	19 ± 1

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error

TABLE G2
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Diethylphthalate[a]

	0 μL	7.5 μL	15 μL	30 μL
Male				
n	10	9	10	9
Hematocrit (%)	43.2 ± 0.9	41.7 ± 0.5	42.6 ± 1.1	42.9 ± 0.7
Hemoglobin (g/dL)	14.8 ± 0.4	14.2 ± 0.2	14.6 ± 0.4	14.7 ± 0.3
Erythrocytes (10^6/μL)	9.32 ± 0.19	8.96 ± 0.11	9.18 ± 0.25	9.30 ± 0.21
Mean cell volume (fL)	46.3 ± 0.2	46.6 ± 0.2	46.5 ± 0.2	46.2 ± 0.4
Mean cell hemoglobin (pg)	15.9 ± 0.1	15.8 ± 0.1	15.9 ± 0.1	15.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.2 ± 0.2	34.0 ± 0.1	34.2 ± 0.2	34.1 ± 0.2
Leukocytes (10^3/μL)	6.20 ± 0.38	5.11 ± 0.33	6.04 ± 0.24	5.42 ± 0.48
Segmented neutrophils (10^3/μL)	1.42 ± 0.26	1.28 ± 0.18	1.61 ± 0.15	1.28 ± 0.27
Lymphocytes (10^3/μL)	4.60 ± 0.28	3.68 ± 0.25	4.33 ± 0.18	4.08 ± 0.29
Monocytes (10^3/μL)	0.09 ± 0.03	0.04 ± 0.02	0.03 ± 0.02	0.00 ± 0.00**
Eosinophils (10^3/μL)	0.09 ± 0.03	0.12 ± 0.04	0.06 ± 0.03	0.07 ± 0.02
Female				
n	10	9	10	10
Hematocrit (%)	40.6 ± 0.8	40.9 ± 0.8	40.5 ± 0.9	40.4 ± 0.7
Hemoglobin (g/dL)	13.8 ± 0.3	13.9 ± 0.3	13.7 ± 0.4	14.0 ± 0.4
Erythrocytes (10^6/μL)	8.69 ± 0.18	8.73 ± 0.20	8.68 ± 0.22	8.69 ± 0.19
Mean cell volume (fL)	46.7 ± 0.2	46.9 ± 0.2	46.7 ± 0.2	46.6 ± 0.4
Mean cell hemoglobin (pg)	15.9 ± 0.1	15.9 ± 0.1	15.8 ± 0.1	16.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.1 ± 0.1	33.9 ± 0.1	33.9 ± 0.2	34.5 ± 0.6
Leukocytes (10^3/μL)	4.30 ± 0.41	4.42 ± 0.37	4.34 ± 0.32	4.22 ± 0.55[b]
Segmented neutrophils (10^3/μL)	0.96 ± 0.12	1.08 ± 0.21	0.90 ± 0.14	1.18 ± 0.24
Lymphocytes (10^3/μL)	3.15 ± 0.31	3.24 ± 0.20	3.31 ± 0.26	3.17 ± 0.39[b]
Monocytes (10^3/μL)	0.05 ± 0.03	0.02 ± 0.02	0.03 ± 0.02	0.03 ± 0.02[b]
Eosinophils (10^3/μL)	0.14 ± 0.05	0.07 ± 0.03	0.07 ± 0.03	0.03 ± 0.02*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION 252
PREPARATION AND ANALYSIS OF DOSE FORMULATIONS 255
FIGURE H1 Infrared Absorption Spectrum of Diethylphthalate 257
FIGURE H2 Nuclear Magnetic Resonance Spectrum of Diethylphthalate 258
FIGURE H3 Infrared Absorption Spectrum of Dimethylphthalate 259
FIGURE H4 Nuclear Magnetic Resonance Spectrum of Dimethylphthalate 260
FIGURE H5 Infrared Absorption Spectrum of 7,12-Dimethylbenz(a)anthracene 261
FIGURE H6 Nuclear Magnetic Resonance Spectrum of 7,12-Dimethylbenz(a)anthracene 262
FIGURE H7 Nuclear Magnetic Resonance Spectrum of 12-*O*-Tetradecanoylphorbol-13-Acetate 263
TABLE H1 Preparation and Storage of Dose Formulations in the Dermal Studies of Diethylphthalate and Dimethylphthalate 264
TABLE H2 Results of Analysis of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Diethylphthalate 265
TABLE H3 Results of Analysis of Dose Formulations Administered to Mice in the 1-Year Dermal Study of Diethylphthalate and Dimethylphthalate 267
TABLE H4 Results of Referee Analysis of Dose Formulations Administered to Mice in the 1-Year Dermal Study of Diethylphthalate and Dimethylphthalate and in the 2-Year Dermal Study of Diethylphthalate 268

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Diethylphthalate

Diethylphthalate was obtained from Tennessee Eastman Company (Kingsport, TN) in one lot (84117), which was used throughout the 4-week dermal studies, 1-year dermal study in male mice, and 2-year dermal studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the diethylphthalate studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a clear colorless liquid, was identified as diethylphthalate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of diethylphthalate (Figures H1 and H2).

The purity was determined by elemental analyses, Karl Fischer water analysis, titration of free acid, ester titration, thin-layer chromatography, and gas chromatography. For free acid titration, samples were dissolved in ethanol, titrated with 0.05 N aqueous sodium hydroxide, and monitored potentiometrically with an electrode filled with 3 M potassium chloride. For ester titration, samples were hydrolyzed with 1.0 N potassium hydroxide, shaken for 16 hours, and titrated with 0.5 N hydrochloric acid. Ester titration was monitored potentiometrically with an electrode filled with 3 M potassium chloride. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) hexane:ethyl acetate (80:20), and 2) methylene chloride:acetone (95:5). Dicyclohexyl phthalate was used as a reference standard. Plates were examined under 254 nm ultraviolet light and a spray of resorcinol-zinc chloride-sulfuric acid. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) 3% SP-2100 on 100/120 Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and

B) 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), with an oven temperature program of 60° C for 6 minutes, then 60° to 200° C at 10° C per minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for diethylphthalate. Karl Fischer water analysis indicated 0.083% ± 0.003% water. Free acid titration indicated less than 0.00006 mEq acid per gram of sample. Ester titration indicated a purity of 100.9% ± 0.3%. Thin-layer chromatography by each system indicated only a major spot. Gas chromatography indicated one major peak and no impurities with areas greater than 0.1% relative to the major peak using either system. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A, except with an isothermal oven temperature of 170° C and 0.2% (w/v) tetradecane added as an internal standard. These studies indicated that diethylphthalate was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically by the study laboratory using gas chromatography and free acid titration methods similar to those described above. No degradation of the bulk chemical was observed.

Dimethylphthalate

Dimethylphthalate was obtained from Chemical Technical Industries (Orlando, FL) in one lot (C122883), which was used during the 1-year dermal study in male mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute. Reports on analyses performed in support of the dimethylphthalate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear colorless liquid, was identified as dimethylphthalate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of dimethylphthalate (Figures H3 and H4).

The purity was determined by elemental analyses, Karl Fischer water analysis, titration of free acid, ester titration, thin-layer chromatography, and gas chromatography. For free acid titration, samples were dissolved in methanol, titrated with 0.01 N aqueous sodium hydroxide, and monitored potentiometrically with an electrode filled with 3 M potassium chloride. For ester titration, samples were hydrolyzed with 0.5 N potassium hydroxide, refluxed for 2 hours, and titrated with 0.5 N hydrochloric acid. Ester titration was monitored potentiometrically with an electrode filled with 3 M potassium chloride. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) hexane:ethyl acetate (80:20), and 2) methylene chloride:acetone (95:5). Dimethylterephthalate was used as a reference standard. Plates were examined under 254 nm and 366 nm ultraviolet light and a spray of resorcinol-zinc chloride-sulfuric acid. Gas chromatography was performed using systems A and B as described in the diethylphthalate purity analysis.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for dimethylphthalate. Karl Fischer water analysis indicated 0.039% ± 0.002% water. Free acid titration indicated 0.00060 ± 0.00004 mEq of acid per g of sample. Ester titration indicated a purity of 99.2% ± 0.8%. Thin-layer chromatography by each system indicated only a major spot. Gas chromatography indicated one major peak and no impurities with areas greater than 0.1% relative to the major peak using both systems. The overall purity was determined to be equal to or greater than 99%.

Stability studies were performed with gas chromatography using system B described previously, except with an isothermal oven temperature of 200° C and 0.1% (w/v) nonadecane added as an internal standard. These studies indicated that dimethylphthalate was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically by the study laboratory using gas chromatography and ester titration methods similar to those described previously. No degradation of the bulk chemical was observed.

7,12-Dimethylbenz(a)anthracene

7,12-Dimethylbenz(a)anthracene was obtained from the Eastman Kodak Company (Rochester, NY) in one lot (K-4). The lot was purified by the analytical chemistry laboratory, Midwest Research Institute. The chemical was dissolved in benzene and then passed through a neutral alumina column. The chemical was crystallized from isopropanol. The purified material was assigned lot number M111384 and was used throughout the 1-year study. Reports on the identity, purity, and stability analyses performed by the analytical chemistry laboratory in support of the 1-year study are on file at the NIEHS.

The chemical, a light yellow powder, was identified as 7,12-dimethylbenz(a)anthracene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of 7,12-dimethylbenz(a)anthracene (Figures H5 and H6).

The purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) toluene:hexane (60:40) and 2) hexane:chloroform (78:22). Plates were examined

under 254 nm and 366 nm ultraviolet light and a spray of 5% (w/v) potassium dichromate in 40% sulfuric acid. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) 3% Dexsil 400 on 80/100 Chromosorb W(AW), with an oven temperature program of 50° C for 5 minutes, then 50° to 300° C at 10° C per minute, and

B) 3% SP-2100 on 100/120 Supelcoport, with an oven temperature program of 75° C for 1 minute, then 75° to 275° C at 10° C per minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for 7,12-dimethylbenz(a)anthracene. Karl Fischer water analysis indicated less than 0.4% water. Thin-layer chromatography by system 1 indicated one major spot and one trace spot, and system 2 indicated only a major spot. Gas chromatography using both systems indicated one major peak and no impurities with peaks greater than 0.1% relative to the major peak area. The overall purity was determined to be greater than 99%.

Stability studies were performed with gas chromatography system A described above except with an isothermal oven temperature of 300° C and 2.3 mg/mL octacosane added as an internal standard. These studies indicated that 7,12-dimethylbenz(a)anthracene was stable as bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically by the study laboratory using ultraviolet spectroscopy and gas chromatography. No degradation of the bulk chemical was observed.

12-*O*-Tetradecanoylphorbol-13-acetate

12-*O*-Tetradecanoylphorbol-13-acetate in sealed vials containing 5 or 10 mg of chemical was obtained from Consolidated Midland Corporation (Brewster, NY) in one lot (031), from Pharmacia PL Biochemical (Milwaukee, WI) in three lots (UN2811, 411999, and OE511999), and from L.C. Services Corporation (Woburn, MA) in one lot (F-121). All five lots were used during the 1-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute. Reports on analyses performed in support of the 1-year study are on file at the NIEHS.

Each lot of the chemical was identified as 12-*O*-tetradecanoylphorbol-13-acetate by nuclear magnetic resonance spectroscopy and mass spectrometry. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of 12-*O*-tetradecanoylphorbol-13-acetate (Figure H7).

The purity of the five lots was determined by thin-layer chromatography and high-performance liquid chromatography. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) anhydrous diethyl ether (100%), and 2) ethyl acetate:chloroform (60:40). Visualization was at 254 nm (and 366 nm for lot 411999) with a spray of 1% (w/v) vanillin in concentrated sulfuric acid, followed by heating at 120° C for 10 to 20 minutes. High-performance liquid chromatography was performed with a DuPont Zorbax ODS column, with a flow rate of 1 mL per minute, detection at 229 nm, and a solvent system of water:acetonitrile (10:90).

Thin-layer chromatography for lots UN2811, OE511999, and F-121 revealed only one major spot using each system. Thin-layer chromatography for lot 411999 revealed only one major spot using system 1 and one major spot and one very slight trace impurity using system 2. Thin-layer chromatography of lot 031 using the first system revealed one major spot, one trace impurity, and one very slight trace impurity, while system 2 revealed one major spot, one trace impurity, one slight trace impurity, and two very slight trace impurities. High-performance liquid chromatography of lot 031 revealed one major peak and 11 impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 3.1% relative to the major peak area. High-performance liquid chromatography of lot UN2811 indicated

one major peak and seven impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 2.9% relative to the major peak area. For lot 411999, high-performance liquid chromatography indicated one major peak and three impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 0.6% relative to the major peak. High-performance liquid chromatography of lot OE511999 indicated one major peak and five impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 1.0% relative to the major peak area. For lot F-121, high-performance liquid chromatography indicated one major peak and two impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 0.8% relative to the major peak area. The overall purity was determined to be 99% for lots F-121, OE511999, and 411999 and 97% for lots 031 and UN2811.

The stability of the chemical was determined using high-performance liquid chromatography system described in the purity analysis. The study indicated that no decomposition had occurred in samples exposed to air and light at ambient temperature for up to 6 days. The study laboratory stored the chemical in sealed vials at –20° C.

Preparation and Analysis of Dose Formulations

Diethylphthalate

In the 4-week studies, 1-year mouse study, and 2-year rat study, the diethylphthalate was applied neat. In the 2-year mouse study, the dose formulations were prepared by mixing diethylphthalate and acetone to give the required concentration (Table H1). The dose formulations were prepared and stored in amber glass bottles at room temperature until 12 December 1986 after which dose formulations were stored in amber glass bottles and refrigerated at 4° C. Dose formulations were discarded 3 weeks after the date of preparation.

Dose formulation stability studies were performed by the analytical chemistry laboratory. Aliquots of the 40 mg/mL formulation of diethylphthalate were mixed with 5 mL of valerophenone (10 mg/mL in water:acetonitrile (40:60, v/v)) and further diluted with water:acetonitrile (40:60, v/v). High-performance liquid chromatography was performed using a Waters μBondapak C_{18} column, with a flow rate of 1 mL/minute, a mobile phase of water:acetonitrile (40:60, v/v), with valerophenone added as an internal standard, and detection at 254 nm. The stability of the diethylphthalate dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark, and for at least 3 hours when exposed to light and air.

Periodic analyses of the dose formulations of diethylphthalate were conducted by the study laboratory and analytical chemistry laboratory using reverse-phase high-performance liquid chromatography. During the 2-year mouse study, the dose formulations were analyzed at least once every 8 weeks (Table H2). In the 2-year mouse study 91% (52/57) of the dose formulations analyzed were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table H4).

Dimethylphthalate

Dimethylphthalate was applied neat in the 1-year mouse study.

7,12-Dimethylbenz-(a)anthracene

In the 1-year mouse study, the dose formulation was prepared by dissolving 7,12-dimethylbenz-(a)anthracene and acetone (w/v) to give the required concentration (Table H1). The dose formulation was stored frozen protected from light, and discarded 3 weeks after preparation.

Stability analyses of the 0.1 mg/mL and 0.0025 mg/mL dose formulations were performed by the analytical chemistry laboratory. Aliquots were diluted with acetone, then mixed with 2 mL of the internal standard

solution, anthracene (50 μg/mL in 85:15, v/v acetonitrile:water), and further diluted with acetonitrile:water (85:15, v/v). High-performance liquid chromatography was performed using a Brownlee RP-18 column, with a flow rate of 1 mL/minute, an a mobile phase of acetonitrile:water (85:15, v/v), with anthracene added as an internal standard, and detection at 365 nm. The stability of the dose formulations was confirmed for up to 3 weeks at room temperature when stored in the dark, and for less than 3 hours when exposed to light and air.

Analysis of the dose formulation of 7,12-dimethylbenz(a)anthracene was conducted by the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy at 363 nm. During the 1-year male mouse study, the dose formulation was analyzed prior to the beginning of the study and was within 10% of the target concentrations (Table H3). Results of referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H4).

12-*O*-Tetradecanoylphorbol-13-acetate

The dose formulations were prepared by mixing 12-*O*-tetradecanoylphorbol-13-acetate and acetone to give the required concentrations (Table H1). Dose formulations were prepared every 2 weeks. The dose formulations were refrigerated in amber glass bottles and were discarded 3 weeks after the date of preparation.

Stability analyses of the acetone solutions were conducted by the analytical chemistry laboratory, using the high-performance liquid chromatography system used in the bulk chemical analyses of 12-*O*-tetradecanoylphorbol-13-acetate except with a Burdick & Jackson C_{18} column and a solvent ratio of 7:93. Stability of the formulation was established for at least 3 weeks when stored at 4° C in amber glass bottles.

Periodic analyses of the dose formulations of 12-*O*-tetradecanoylphorbol-13-acetate were conducted by the study laboratory and by the analytical chemistry laboratory with the same high-performance liquid chromatography method as that used in the stability study except that a solvent ratio of 10:90 was also used. In the study, only 54% (7/13) of the formulations analyzed were within 10% of the target concentrations but with no formulation greater than 26% from the target (Table H3). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated reasonable agreement with the results obtained by the study laboratory (Table H4).

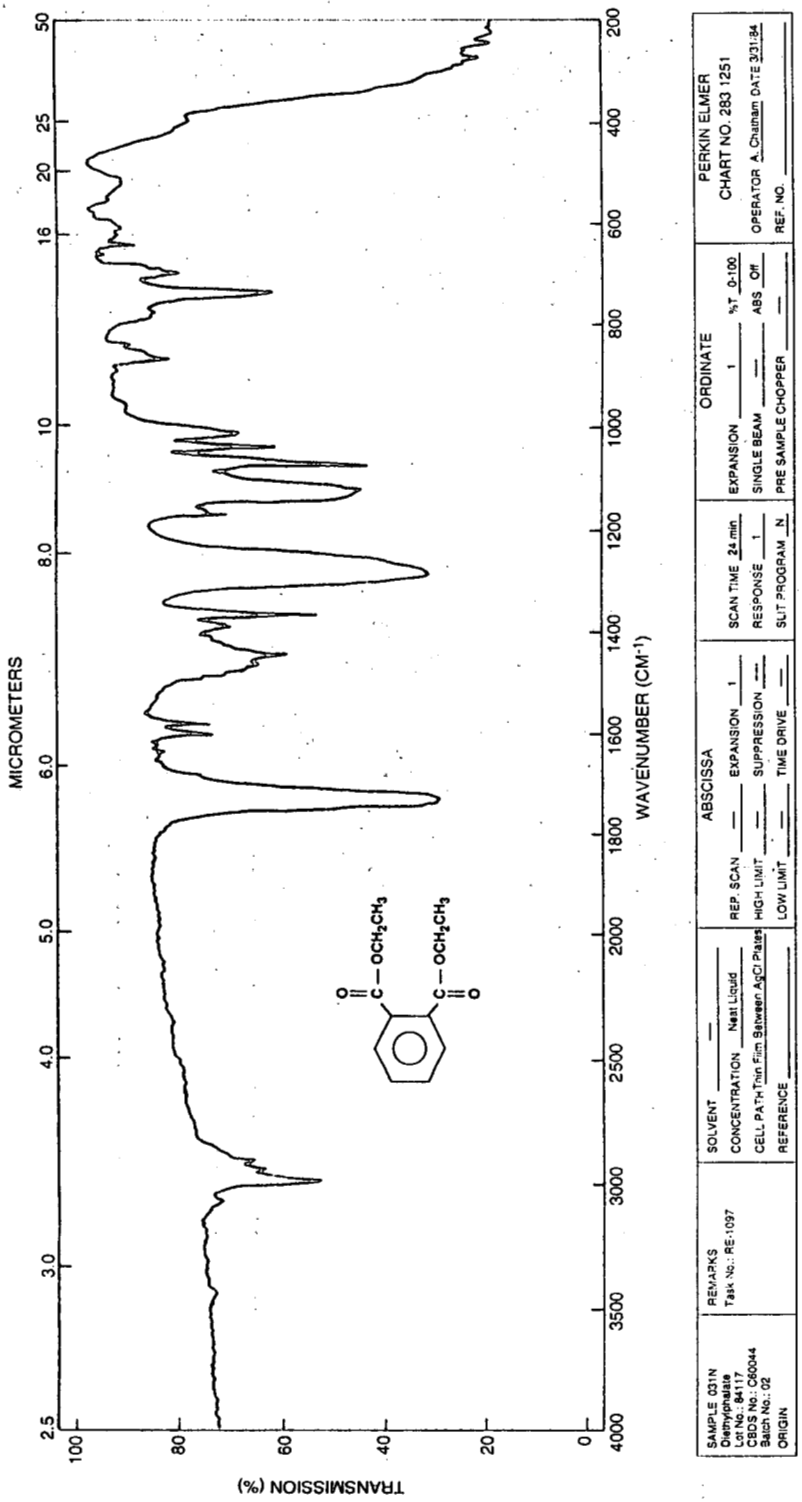


FIGURE H1
Infrared Absorption Spectrum of Diethylphthalate

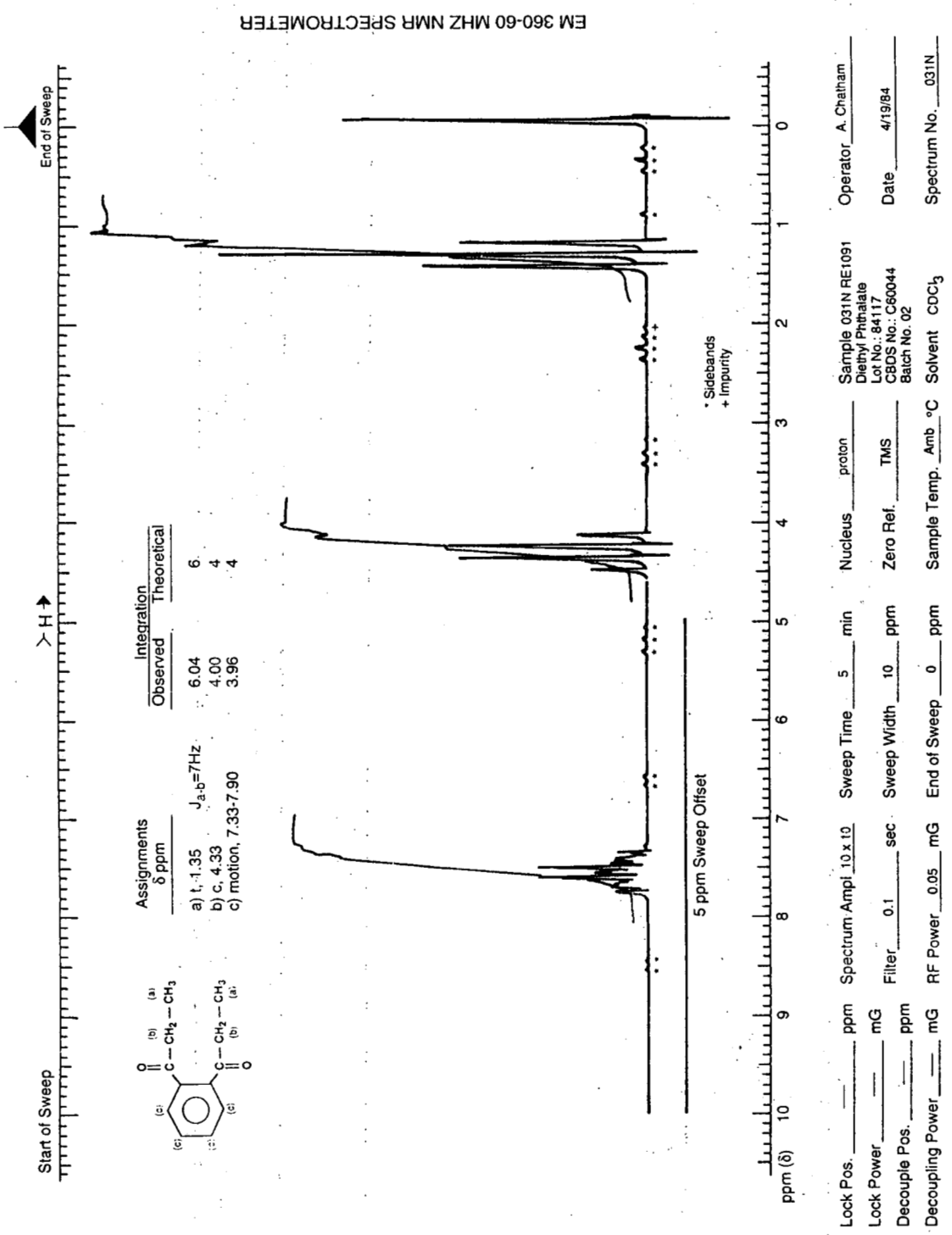


FIGURE H2
Nuclear Magnetic Resonance Spectrum of Diethylphthalate

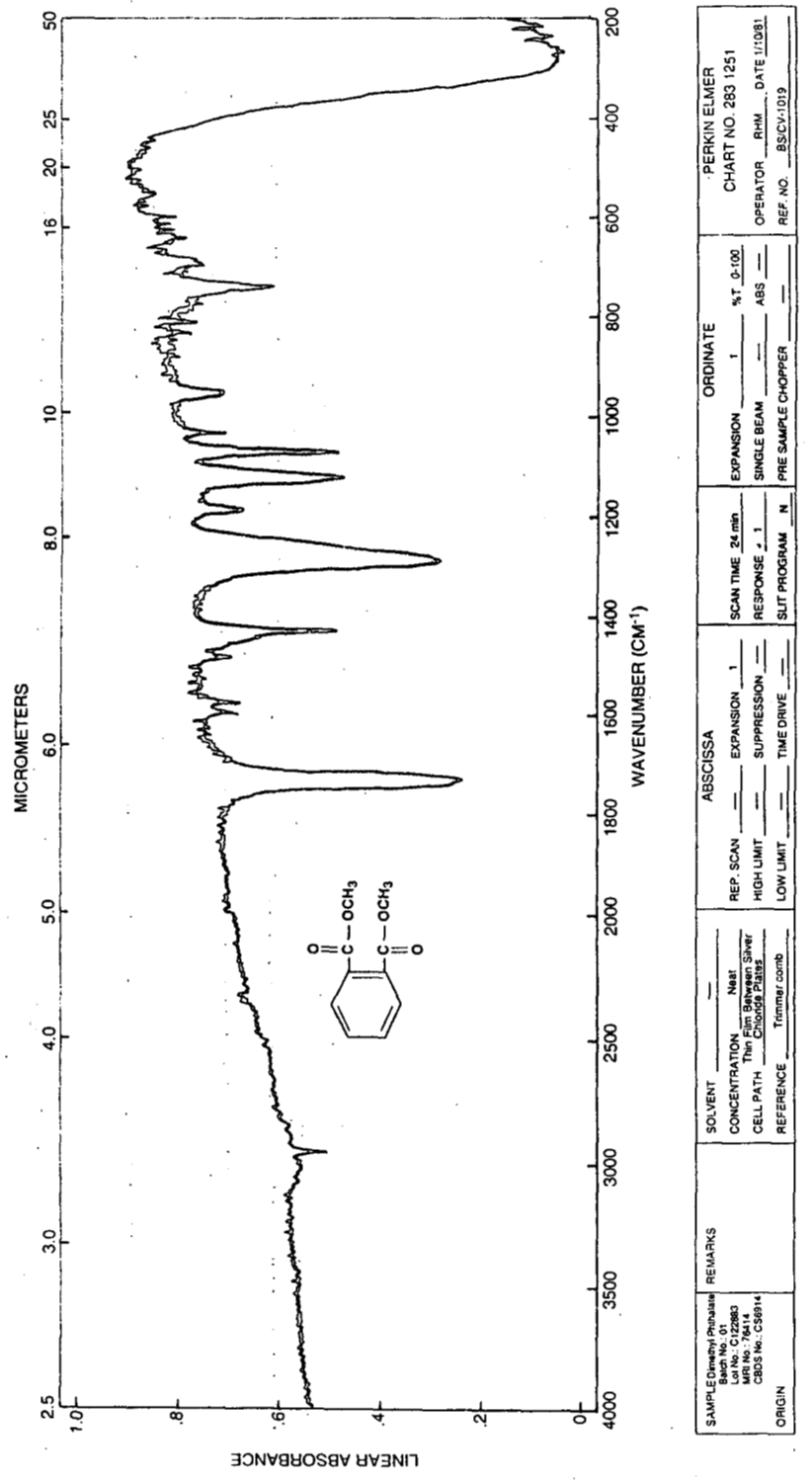


FIGURE H3
Infrared Absorption Spectrum of Dimethylphthalate

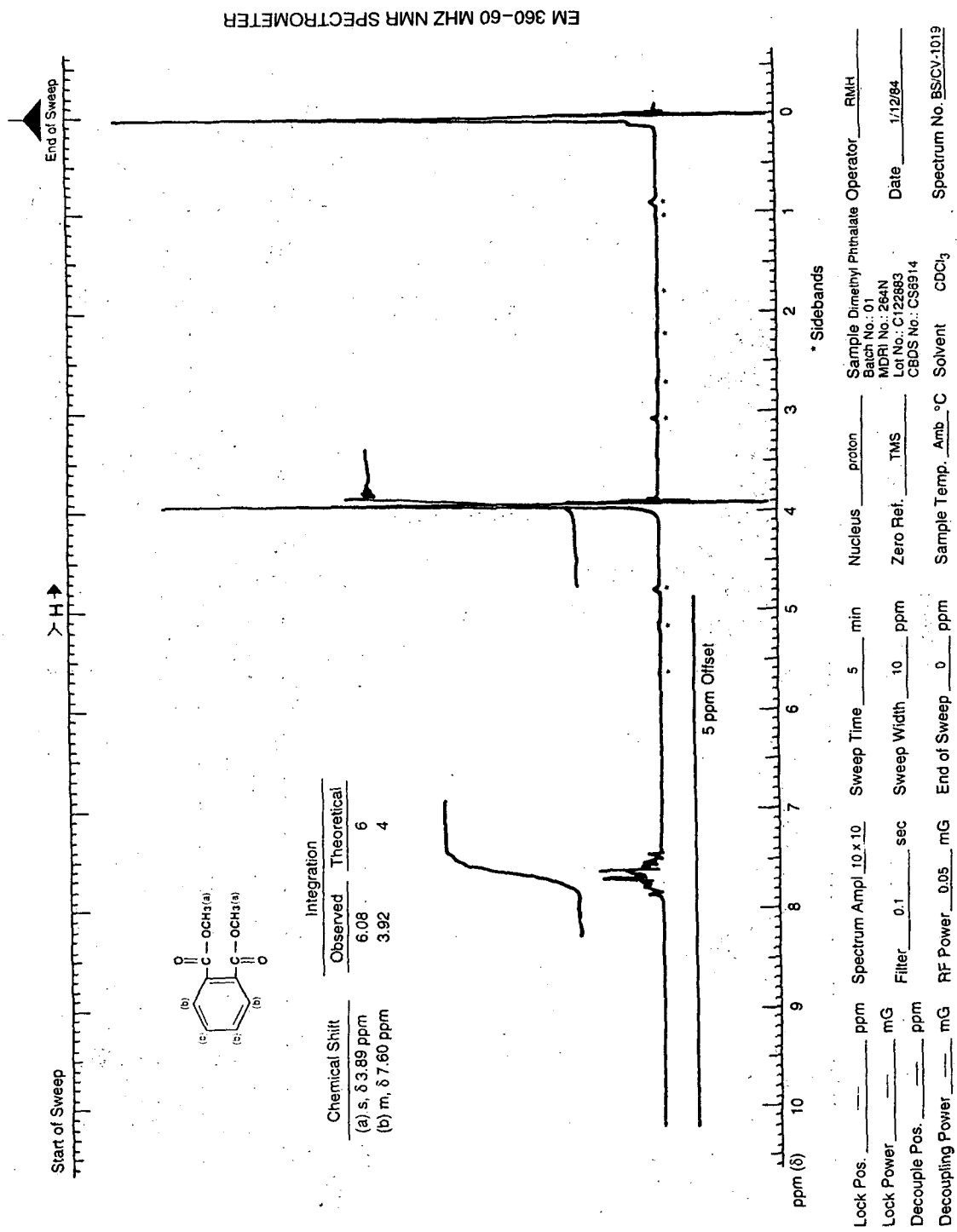


FIGURE H4
Nuclear Magnetic Resonance Spectrum of Dimethylphthalate

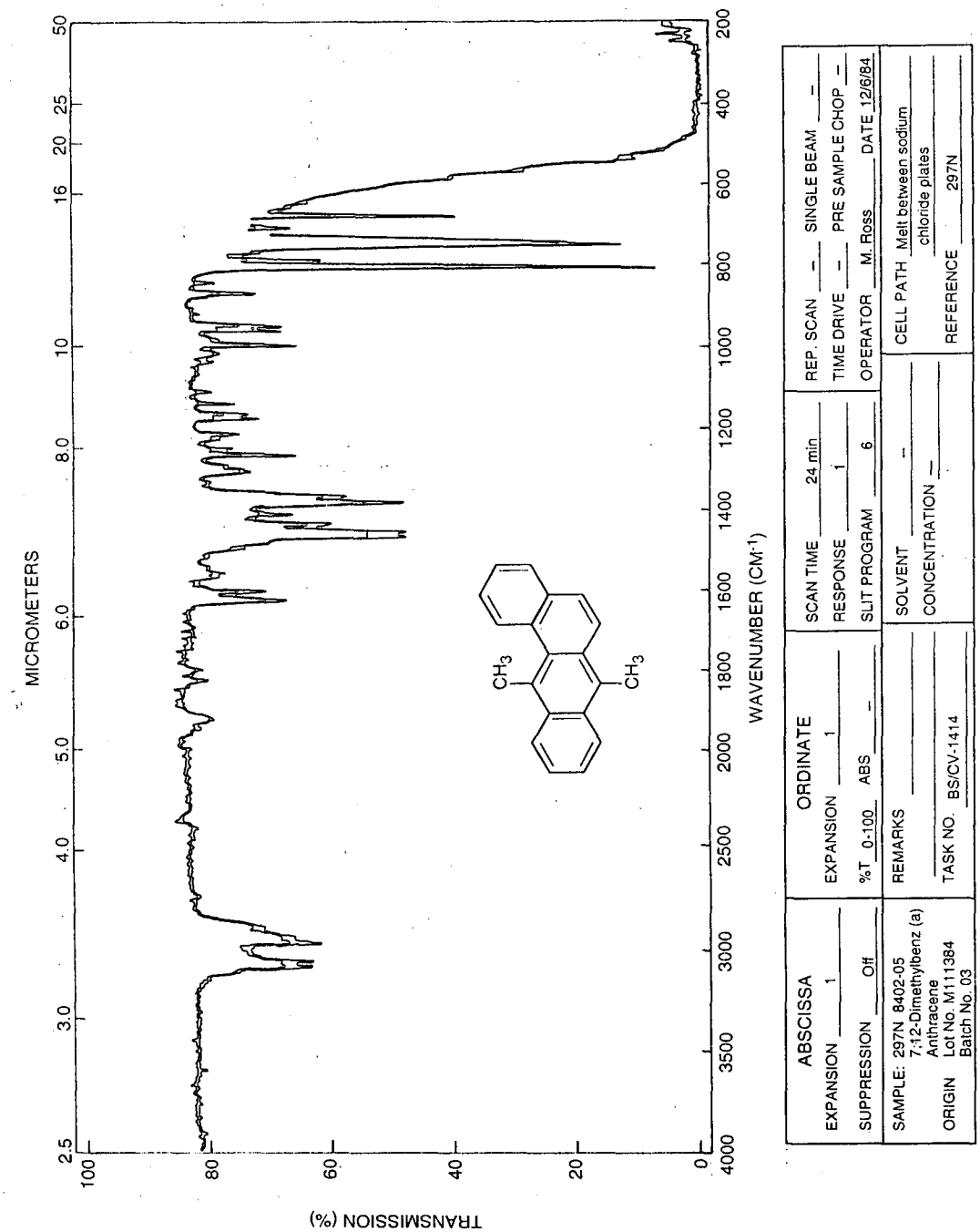


FIGURE H5
Infrared Absorption Spectrum of 7,12-Dimethylbenz(a)anthracene

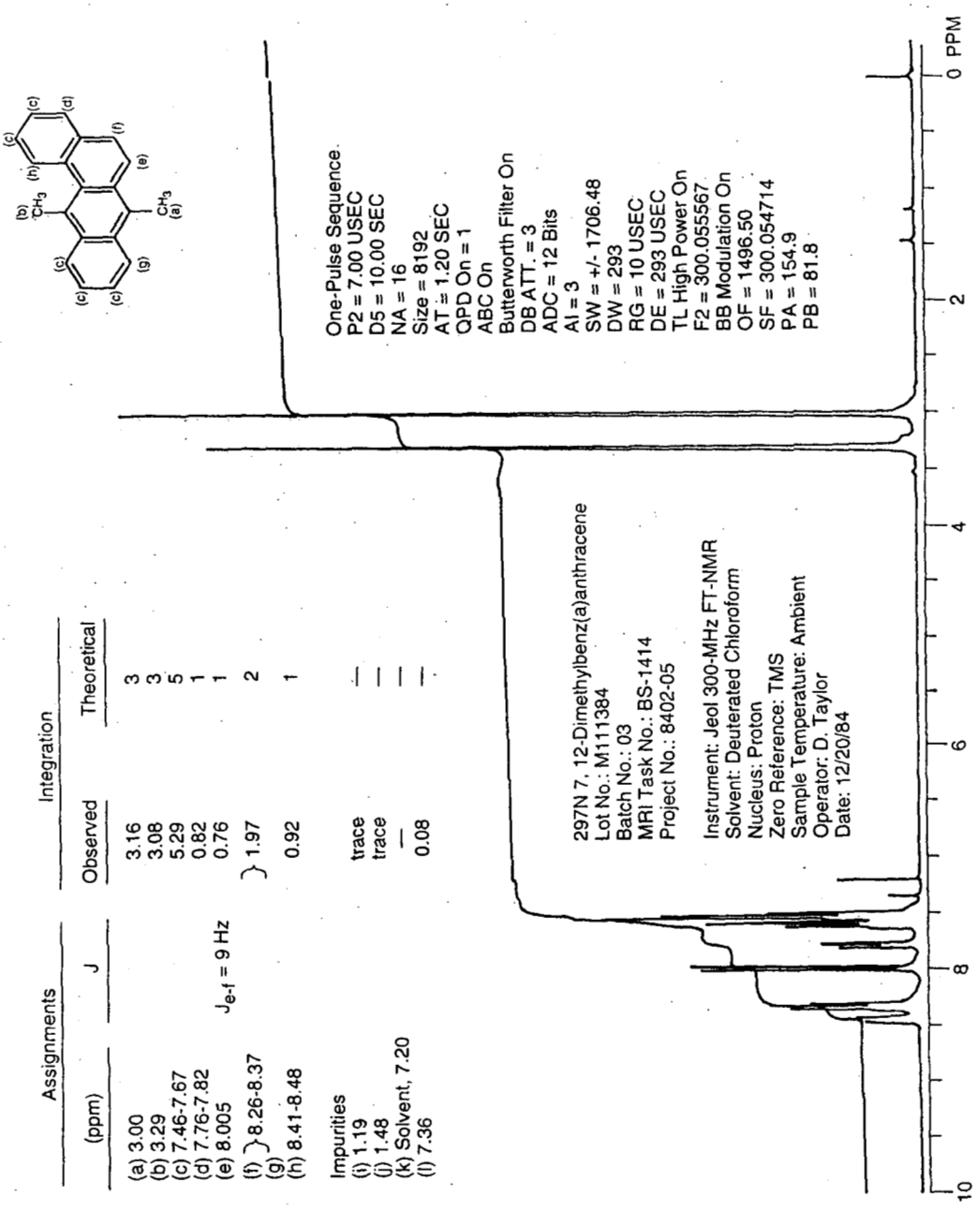


FIGURE H6
Nuclear Magnetic Resonance Spectrum of 7,12-Dimethylbenz(a)anthracene

196N 12-0-Tetradecanoylphorbol-13-acetate
Lot No.: 31
Batch No.: 05
MRI Task No.: BS-1435
Project No.: 8403-05

Instrument: Jeol 300-MHz FT-NMR
Solvent: Deuterated benzene
Nucleus: Proton
Internal Reference: Benzene
Sample Temperature: Ambient
Date: 1/31/85

One-Pulse Sequence
P2 = 7.00 USEC
D5 = 10.00 SEC
NA = 32
Size = 16384
AT = 2.05 SEC
QPD On = 1
ABC On
Butterworth Filter On
DB ATT. = 3
ADC = 12 Bits
AI = 4
SW = +/- 2000.00
DW = 250
RG = 10 USEC
DE = 250 USEC
TL High Power On
F2 = 300.05720
BB Modulation On
OF = 1283.73
SF = 300.054496
PA = 144.8
PB = 89.1

Assignments (δ ppm)	J	Integration	
		Observed	Theoretical
(a) 0.92	$J_{a\text{-}c}$ = 7 Hz	2.97	3
(b) 1.05-1.42		27.48	4
(c) 1.30			22
(d) 1.38		2.89	3
(e) 1.49-1.65		5.95	7
(f) 1.75		2.97	3
(g) 2.19	$J_{c\text{-}g}$ = 7 Hz	1.98	2
(h) 2.38-2.54		2.89	1
(i) 2.50			2
(j) 2.76		0.99	1
(k) 3.41-3.50		1.98	2
(l) 3.80		1.98	2
(m) 5.74		0.99	1
(n) 5.88-5.98		1.98	2
(o) 7.45		0.99	1
(p) 0.65, impurity		0.28	—
(q) 7.15, solvent		—	—

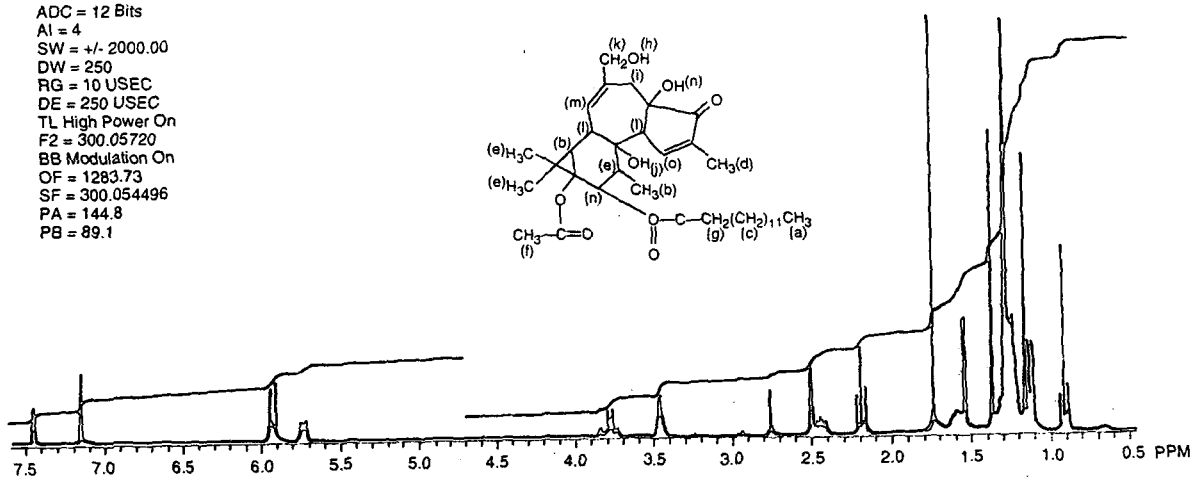


FIGURE H7
Nuclear Magnetic Resonance Spectrum of 12-*O*-Tetradecanoylphorbol-13-acetate

TABLE H1
Preparation and Storage of Dose Formulations in the Dermal Studies of Diethylphthalate and Dimethylphthalate

Diethylphthalate and Dimethylphthalate	7,12-Dimethylbenz(a)anthracene	12-*O*-Tetradecanoylphorbol-13-acetate
Preparation		
Diethylphthalate: Diethylphthalate was applied neat in the 4-week studies, 1-year mouse study, and 2-year rat study. In the 2-year mouse study, the appropriate amount of diethylphthalate was weighed and then mixed with acetone in a graduated cylinder. Acetone was added to obtain a solution with the appropriate diethylphthalate concentration.	The appropriate amount of 7,12-dimethylbenz(a)anthracene was weighed onto weighing paper and then transferred to a graduated cylinder. Residual chemical on the paper was rinsed with acetone and rinses were transferred to the graduated cylinder. Acetone was added to obtain a solution with the appropriate 7,12-dimethylbenz(a)-anthracene concentration.	Vials containing 12-*O*-tetradecanoyl-phorbol-13-acetate were filled with acetone and agitated. The mixture was transferred to a graduated cylinder and each vial was rinsed with acetone. The rinses were transferred to the graduated cylinder. Acetone was added to obtain a solution with the appropriate concentration of 12-*O*-tetradecanoylphorbol-13-acetate/mL acetone.
Dimethylphthalate: Dimethylphthalate was applied neat in the 1-year mouse study.		
Chemical Lot Number		
Diethylphthalate: 84117 **Dimethylphthalate:** C122883	M111384	031, 411999, UN2811, OE511999, and F-121
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
Storage Conditions		
Stored at room temperaure in an amber glass bottle until 12 December 1986 and then at 4° C in an amber glass bottle	Stored at 4° C in an amber glass bottle	Stored at 4° C in an amber glass bottle
Study Laboratory		
Hazleton Laboratories (Rockville, MD)	Hazleton Laboratories (Rockville, MD)	Hazleton Laboratories (Rockville, MD)
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE H2
Results of Analysis of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Diethylphthalate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)[a]	Determined Concentration[b] (mg/mL)	% Difference from Target
15 December 1986	17 December 1986	84.0	84.7	+1
		168	165	–2
		336	360	+7
	31 December 1986[c]	84.0	96.1	+14
		168	183	+9
		336	401	+19
9 February 1987	13 February 1987	84.0	82.5	–2
		168	165	–2
		336	337	0
6 April 1987	9 April 1987	84.0	82.8	–1
		168	160	–5
		336	321	–4
1 June 1987	4 June 1987	84.0	82.6	–2
		168	165	–2
		336	328	–2
	18 June 1987[c]	84.0	83.5	–1
		168	168	0
		336	329	–2
27 July 1987	29 July 1987	84.0	82.6	–2
		168	169	+1
		336	327	–3
21 September 1987	23 September 1987	84.0	81.6	–3
		168	159	–5
		336	314	–7
16 November 1987	20 November 1987	84.0	86.2	+3
		168	170	+1
		336	340	+1
	7 December 1987[c]	84.0	102	+21
		168	204	+21
		336	400	+19
11 January 1988	13 January 1988	84.0	85.3	+2
		168	170	+1
		336	338	+1
7 March 1988	8 March 1988	84.0	84.7	+1
		168	166	–1
		336	331	–1

TABLE H2
Results of Analysis of Dose Formulations Administered to Mice in the 2-Year Dermal Study of Diethylphthalate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
2 May 1988	4 May 1988	84.0	86.3	+3
		168	168	0
		336	335	0
	17 May 1988[c]	84.0	91.0	+8
		168	180	+7
		336	356	+6
27 June 1988	29 June 1988	84.0	83.0	−1
		168	167	−1
		336	334	−1
22 August 1988	23 August 1988	84.0	85.8	+2
		168	167	−1
		336	344	+2
17 October 1988	20 October 1988	84.0	84.3	0
		168	168	0
		336	333	−1
	2 November 1988[c]	84.0	88.0	+5
		168	173	+3
		336	344	+2
12 December 1988	14 December 1988	84.0	83.1	−1
		168	167	−1
		336	334	−1

[a] Dosing volume = 0.1 mL; 84.0 mg/mL = 7.5 μL/0.1 mL; 168 mg/mL = 15 μL/0.1 mL; 336 mg/mL = 30 μL/0.1 mL
[b] Results of duplicate analyses
[c] Animal room samples

TABLE H3
Results of Analysis of Dose Formulations Administered to Mice in the 1-Year Dermal Study of Diethylphthalate and Dimethylphthalate

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	% Difference from Target
7,12-Dimethylbenz(a)anthracene				
31 July 1985	31 July 1985	0.5	0.524	+5
12-*O*-Tetradecanoylphorbol-13-acetate				
7 August 1985	7 August 1985[c]	0.05	0.059	+18
8 August 1985	8 August 1985	0.05	0.0506	+1
	26 August 1985[d]	0.05	0.0491	–2
30 September 1985	1 October 1985	0.05	0.0483	–3
9 December 1985	12 December 1985	0.025	0.0263	+5
3 February 1986	6 February 1986[e]	0.025	0.0314	+26
	19 February 1986	0.025	0.0289	+16
7 April 1986	9 April 1986	0.025	0.0216	–14[f]
14 April 1986	15 April 1986[g]	0.025	0.0273	+9
9 June 1986	12 June 1986	0.025	0.0242	–3
4 August 1986	5 August 1986	0.025	0.0206	–18[f]
6 August 1986	6 August 1986[g]	0.025	0.0201	–20[h]
	12 August 1986[i]	0.025	0.0242	–3

[a] Dosing volume = 0.1 mL
[b] Results of duplicate analyses
[c] Volume of solution was adjusted to the appropriate concentration and resubmitted for analysis.
[d] Sample of the adjusted formulation of 7 August 1985
[e] At the time of analysis the sample was calculated to be within target. On 12 February 1986, a calculation error was discovered resulting in the percent target exceeding 10%.
[f] Sample remixed
[g] Result of remix
[h] Sample reanalyzed
[i] Result of reanalysis

TABLE H4
Results of Referee Analysis of Dose Formulations Administered to Mice in the 1-Year Dermal Study of Diethylphthalate and Dimethylphthalate and in the 2-Year Dermal Study of Diethylphthalate

Date Mixed	Target Concentration (mg/mL)[a]	Determined Concentration (mg/mL)	
		Study Laboratory[b]	Referee Laboratory
1-Year Study			
7,12-Dimethylbenz(a)anthracene			
31 July 1985	0.5	0.524	0.515 ± 0.003
12-*O*-Tetradecanoylphorbol-13-acetate			
8 August 1985	0.05	0.0506	0.0472 ± 0.0001
3 February 1986	0.025	0.0314	0.0280 ± 0.0001
6 August 1986	0.025	0.0201	0.0214 ± 0.0002
2-Year Studies			
Diethylphthalate			
15 December 1986	168	165	166 ± 2
1 June 1987	84	83.5	82.4 ± 0.1
16 November 1987	336	340	341 ± 4
2 May 1988	84	86.3	87.2 ± 0.3
17 October 1988	168	168	168 ± 0.0

[a] Dosing volume (diethylphthalate only) = 0.1 mL; 84.0 mg/mL = 7.5 μL/0.1 mL; 168 mg/mL = 15 μL/0.1 mL; 336 mg/mL = 30 μL/0.1 mL
[b] Results of duplicate analyses

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

TABLE I1	Ingredients of NIH-07 Rat and Mouse Ration	270
TABLE I2	Vitamins and Minerals in NIH-07 Rat and Mouse Ration	270
TABLE I3	Nutrient Composition of NIH-07 Rat and Mouse Ration	271
TABLE I4	Contaminant Levels in NIH-07 Rat and Mouse Ration	272

TABLE I1
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 I2
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 I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.40 ± 0.82	21.10 – 24.40	30
Crude Fat (% by weight)	5.52 ± 0.37	4.70 – 6.40	30
Crude Fiber (% by weight)	3.42 ± 0.22	3.00 – 3.90	30
Ash (% by weight)	6.67 ± 0.33	6.16 – 7.27	30
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 – 1.390	10
Cystine	0.306 ± 0.075	0.181 – 0.400	10
Glycine	1.160 ± 0.050	1.060 – 1.220	10
Histidine	0.580 ± 0.024	0.531 – 0.608	10
Isoleucine	0.917 ± 0.034	0.867 – 0.965	10
Leucine	1.972 ± 0.052	1.850 – 2.040	10
Lysine	1.273 ± 0.051	1.200 – 1.370	10
Methionine	0.437 ± 0.115	0.306 – 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 – 1.110	10
Threonine	0.896 ± 0.055	0.824 – 0.985	10
Tryptophan	0.223 ± 0.160	0.107 – 0.671	10
Tyrosine	0.677 ± 0.105	0.564 – 0.794	10
Valine	1.089 ± 0.057	0.962 – 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 – 2.570	9
Linolenic	0.277 ± 0.036	0.210 – 0.320	9
Vitamins			
Vitamin A (IU/kg)	7,514 ± 2,140	4,700 – 13,000	30
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 – 48.9	9
Thiamine (ppm)	20.33 ± 2.56	15.0 – 25.0	30
Riboflavin (ppm)	7.92 ± 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 – 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 – 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 – 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 – 65.0	10
Choline (ppm)	3,608 ± 314	2,400 – 3,430	9
Minerals			
Calcium (%)	1.17 ± 0.11	1.00 – 1.40	17
Phosphorus (%)	0.93 ± 0.03	0.87 – 1.00	17
Potassium (%)	0.887 ± 0.067	0.772 – 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 – 1.150	6

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.30	0.05 – 1.07	30
Cadmium (ppm)	<0.10		30
Lead (ppm)	0.40 ± 0.29	0.05 – 1.32	30
Mercury (ppm)[b]	0.05 ± 0.01	0.05 – 0.08	30
Selenium (ppm)	0.34 ± 0.10	0.17 – 0.60	30
Aflatoxins (ppb)	<5.0		30
Nitrate nitrogen (ppm)[c]	17.34 ± 7.80	0.30 – 33.0	30
Nitrite nitrogen (ppm)[c]	0.39 ± 0.67	<0.10 – 2.60	30
BHA (ppm)[d]	2.93 ± 3.70	<2.00 – 22.0	30
BHT (ppm)[d]	1.43 ± 0.90	<1.00 – 4.00	30
Aerobic plate count (CFU/g)[e]	167,036 ± 268,205	3,400 – 1,200,000	30
Coliform (MPN/g)[f]	101 ± 218	<3.00 – 1,100	30
E. coli (MPN/g)[g]	3.03 ± 0.18	<3.00 – 4.00	30
Total nitrosoamines (ppb)[h]	8.97 ± 3.83	3.80 – 19.40	30
N-Nitrosodimethylamine (ppb)[h]	7.25 ± 3.32	2.80 – 15.00	30
N-Nitrosopyrrolidine (ppb)[h]	1.72 ± 1.32	1.00 – 5.40	30
Pesticides (ppm)			
α-BHC[i]	<0.01		30
ß-BHC	<0.02		30
γ-BHC	<0.01		30
δ-BHC	<0.01		30
Heptachlor	<0.01		30
Aldrin	<0.01		30
Heptachlor epoxide	<0.01		30
DDE	<0.01		30
DDD	<0.01		30
DDT	<0.01		30
HCB	<0.01		30
Mirex	<0.01		30
Methoxychlor	<0.05		30
Dieldrin	<0.01		30
Endrin	<0.01		30
Telodrin	<0.01		30
Chlordane	<0.05		30
Toxaphene	<0.1		30
Estimated PCBs	<0.2		30
Ronnel	<0.01		30
Ethion	<0.02		30
Trithion	<0.05		30
Diazinon	<0.1		30
Methyl parathion	<0.02		30
Ethyl parathion	<0.02		30
Malathion	0.10 ± 0.09	0.05 – 0.37	30
Endosulfan I	<0.01		30
Endosulfan II	<0.01		30
Endosulfan sulfate	<0.03		30

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] One lot milled 3 September 1986 contained 0.08 ppm; all other lots were less than or equal to the detection limit.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming unit
[f] MPN = most probable number
[g] One lot milled 4 April 1988 contained 4.0 MPN; all other lots were less than or equal to the detection limit.
[h] All values were corrected for percent recovery.
[i] BHC is hexachlorocyclohexane or benzene hexachloride

APPENDIX J
SENTINEL ANIMAL PROGRAM

METHODS 276
TABLE J1 Murine Virus Antibody Determinations for Swiss (CD-1®) Mice in the 1-Year Initiation/Promotion Study of Diethylphthalate/Dimethylphthalate and for B6C3F$_1$ Mice in the 2-Year Dermal Study of Diethylphthalate 278

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 are untreated, and 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.

Rats

During the 2-year study, 15 male and 15 female F344/N rats were maintained with the study animals to serve as sentinel animals. Samples for viral screening were collected from five male and five female sentinel rats at 6, 12, and 18 months into the study. Samples for the 24-month screening were collected from five male and five female treated rats. These samples were processed appropriately and submitted to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
CARB (cilia-associated respiratory bacillus)	18 months
Mycoplasma arthritidis	6, 12, 18, and 24 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
KRV (Kilham rat virus)	6, 12, 18, and 24 months

All test results for rats were negative.

Mice

For the 1-year initiation/promotion study, 10 male Swiss (CD-1®) mice were maintained with the study animals to serve as sentinel animals. Serum samples for viral screening were collected from five sentinel mice at 6 and 12 months. Blood from each collection was processed appropriately, shipped to Microbiological Associates, Inc., and screened for the following:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	6 and 12 months

Method of Analysis (continued)	Time of Analysis (continued)
ELISA	
CARB	12 months
Ectromelia virus	6 and 12 months
GDVII (mouse encephalomyelitis virus)	6 and 12 months
M. arthritidis	6 and 12 months
M. pulmonis	6 and 12 months
MHV (mouse hepatitis virus)	6 and 12 months
Mouse adenoma virus	6 and 12 months
PVM	6 and 12 months
Reovirus 3	6 and 12 months
Sendai	6 and 12 months
Hemagglutination Inhibition	
K (papovavirus)	6 and 12 months
MVM (minute virus of mice)	6 and 12 months
Polyoma virus	6 and 12 months
Immunofluorescent Antibody	
EDIM (epizootic diarrhea of infant mice)	6 and 12 months
Mouse adenoma virus	12 months

During the 2-year study, 15 male and 15 female B6C3F$_1$ mice were maintained with the study animals to serve as sentinel animals. Samples for viral screening were collected from five male and five female sentinel mice at 6, 12, and 18 months into the study. Samples for the 24-month screening were obtained from five male and five female treated mice. Blood from each collection was processed appropriately and submitted to Microbiological Associates to be screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
LCM	6, 12, and 18 months
M. arthritidis	24 months
M. pulmonis	24 months
MHV	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MVM	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
Immunofluorescent Antibody	
EDIM	6, 12, 18, and 24 months
LCM	24 months
Reovirus 3	18 months

Test results are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Swiss (CD-1®) Mice in the 1-Year Initiation/Promotion Study of Diethylphthalate/Dimethylphthalate and for B6C3F$_1$ Mice in the 2-Year Dermal Study of Diethylphthalate

	Interval (months)	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
1-Year Study			
Swiss (CD-1®) Males	6 months	0/5	None positive
	12 months	1/5	Mouse adenoma virus
		3/5	*M. arthritidis*
		1/5	EDIM
2-Year Study			
B6C3F$_1$ Males	6 months	0/5	None positive
	12 months	2/5	EDIM
	18 months	4/5	EDIM
	24 months	5/5	EDIM
B6C3F$_1$ Females	6 months	0/5	None positive
	12 months	3/5	EDIM
	18 months	1/5	EDIM
		2/5	Reovirus 3
	24 months	1/5	EDIM

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF MAY 1995

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene

TR No.	CHEMICAL
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate & Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

☆ U.S. GOVERNMENT PRINTING OFFICE : 1995 O - 398-121

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF MAY 1995 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	*Tetracycline Hydrochloride*
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	α-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
384	1,2,3-Trichloropropane
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
426	Corn Oil, Safflower Oil, and Tricaprylin
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
430	C.I. Direct Blue 218
431	Benzyl Acetate
432	Barium Chloride Dihydrate
433	Tricresyl Phosphate
434	1,3-Butadiene
435	4,4′-Thiobis(6-*t*-butyl-*m*-cresol)
437	Hexachlorocyclopentadiene
440	Ozone and Ozone/NNK
442	*p*-Nitrobenzoic Acid
443	Oxazepam

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

SPECIAL FOURTH-CLASS RATE
POSTAGE AND FEES PAID
DHHS/NIH
Permit No. G-763

Official Business
Penalty for Private Use - $300

NIH Publication No. 95-3356
May 1995