NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 242

CARCINOGENESIS BIOASSAY OF DIALLYL PHTHALATE (CAS NO. 131-17-9) IN B6C3F$_1$ MICE (GAVAGE STUDY)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOASSAY OF DIALLYL PHTHALATE (CAS. NO. 131-17-9)

IN B6C3F1 MICE (GAVAGE STUDY)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709
and
Bethesda, Maryland 20205

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Public Health Service
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NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program 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. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

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 carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

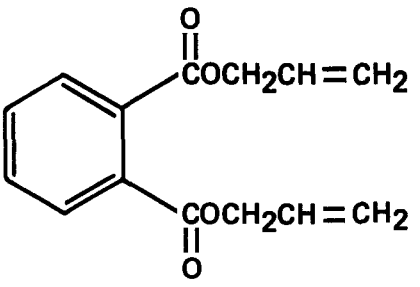
TABLE OF CONTENTS

TABLES

FIGURES

APPENDIXES

CARCINOGENESIS BIOASSAY OF DIALLYL PHTHALATE



DIALLYL PHTHALATE

CAS NO. 131-17-9
$C_{14}H_{14}O_4$ Mol. Wt. 246.24

ABSTRACT

A carcinogenesis bioassay of diallyl phthalate (99% pure) was conducted by administering 0 (vehicle control), 150, or 300 mg/kg diallyl phthalate in corn oil by gavage, 5 days per week for 103 weeks, to groups of 50 male and 50 female B6C3F$_1$ mice. Survival rates and mean body weights of dosed mice were not different from those of controls, and pathological lesions unrelated to proliferative changes were not observed. Therefore, a maximally tolerated dose for the purposes of carcinogenicity testing may not have been achieved.

The incidences of lymphoma and either lymphoma or leukemia in dosed male mice were not significantly greater than those in the controls according to pairwise comparisons (P=0.051 to P=0.096), but the trend tests were statistically significant by either life table or incidental tumor analyses (P=0.031 to P=0.045). The incidence of lymphomas in the high-dose male mice was 12/50 (24%) in comparison with 6/50 (12%) in the controls. Recent historical incidences at the performing laboratory and in the NTP Bioassay Program were 18/120 (15%) and 71/661 (11%), respectively. Since the incidence of high-dose male mice with leukemia was not significantly greater than that of concurrent or historical controls at the performing laboratory by pairwise comparisons, this marginal increase was considered only to be equivocally related to diallyl phthalate administration.

Increased incidences of squamous cell papillomas, hyperplasia, and inflammatory lesions of the forestomach were observed in diallyl phthalate-dosed mice of both sexes in a dose-related manner. Papillomas of the forestomach were observed in 0%, 2%, and 4% of the control, low-dose, and high-dose mice of both sexes. The recent historical incidence of this tumor in gavage control mice from both the performing laboratory and other laboratories within the Bioassay Program was less than 1%. Forestomach hyperplasia was diagnosed in 0%, 15%, and 18%, and in 8%, 2%, and 29% of the control, low-dose, and high-dose male and female mice, respectively; chronic inflammation of the forestomach was diagnosed in 0%, 9%, and 16% and in 4%, 2%, and 18% of the control, low-dose, and high-dose male and female mice, respectively. Because of the numerical elevation of forestomach papillomas in high-dose mice of both sexes, the concomitant observation of dose-related forestomach hyperplasia, and the rarity of this tumor in corn oil (gavage) control B6C3F$_1$ mice, the development of squamous cell papillomas of the forestomach may have been related to diallyl phthalate administration.

Under the conditions of this bioassay, the development of chronic inflammation and hyperplasia of the forestomach in both male and female $B6C3F_1$ mice was considered to be related to the administration of diallyl phthalate. The development of squamous cell papillomas of the forestomach may also have been related to chemical administration, but the available data are insufficient to indicate a clear cause and effect relationship. An increase in the incidence of male mice with lymphomas was observed, but this increase was considered only to be equivocally related to diallyl phthalate administration. The results of this bioassay, therefore, do not indicate that diallyl phthalate is carcinogenic in $B6C3F_1$ mice, although a maximal tolerated dose may not have been achieved. A carcinogenicity study by the National Toxicology Program of diallyl phthalate in male and female Fischer 344/N rats, employing daily gavage doses of 0 (vehicle control), 50, or 100 mg/kg body weight, is currently being evaluated.

CONTRIBUTORS

The bioassay of diallyl phthalate was conducted at Litton Bionetics, Inc., under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year study was begun in September 1978 and was completed in September 1980.

Principal Contributors at Litton Bionetics, Inc.
5516 Nicholson Lane
Kensington, Maryland 20795
(Conducted bioassay and evaluated tissues)

Dr. G. Parker
Pathologist

Dr. E. Gordon
Principal Investigator

Dr. C. Johnston
Principal Investigator

Ms. Helena Jacobs
Group Leader

Dr. A. Manus
Principal Investigator

Principal Contributors at Tracor Jitco
1776 East Jefferson Street
Rockville, Maryland 20852
and
P. O. Box 12358
Research Triangle Park
North Carolina 27709
(Prepared preliminary technical report)

Dr. J. Keller
Director, Bioassay

Dr. S. Olin
Program Associate Director

Mr. E. Cremmins
Technical Editor

Ms. C. Dean
Production Editor

Dr. A. Jacobs
Bioscience Writer

Ms. M. Levy
Technical Editor

Dr. M. Stedham
Pathologist

Dr. W. Theriault
Reports Manager

Dr. J. Tomaszewski
Chemist

Mr. J. Warner
Statistician

Principal Contributors at the National Toxicology Program

National Institute of Environmental Health Sciences
Research Triangle Park
Box 12233
North Carolina 27709
and
Bethesda, Maryland 20205
(Evaluated experiment, interpreted
results, and reported findings)

Dr. W. Kluwe (Chemical Manager)
Dr. Gary A. Boorman
Dr. Rajendra S. Chhabra
Dr. Michael P. Dieter
Dr. J. F. Douglas
Dr. Charles K. Grieshaber
Dr. Larry Hart
Dr. Joseph Haseman
Dr. James Huff
Dr. C. W. Jameson
Dr. Ernest E. McConnell
Dr. John A. Moore
Dr. Raymond Tennant

The pathology report and selected slides were evaluated in June 1981 by the NTP Pathology Working Group, which included Drs. J. Ward, G. Reznik, and M. Stedham (Tracor Jitco).

The chemicals used in this bioassay of diallyl phthalate were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analyses of chemical/vehicle mixtures were done by Litton Bionetics, Inc.

REVIEWERS

National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee

Margaret Hitchcock, Ph.D (Chairperson)
Pharmacology Toxicology
John B. Pierce Foundation Laboratory
New Haven, Connecticut

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
University of North Carolina
Chapel Hill, North Carolina

Alice Whittemore, Ph.D.*
Biostatistics
Stanford University School of Medicine
Palo Alto, California

Ad Hoc Subcommittee Panel of Experts

Norman Breslow, Ph.D. (Principal Reviewer)
Biostatistics
University of Washington
Seattle, Washington

Robert M. Elashoff, Ph.D.
Biostatistics
University of California at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Joseph Highland, Ph.D.
Toxicology
Environmental Defense Fund
Washington, D.C.

J. Michael Holland, Ph.D., D.V.M.
(Principal Reviewer)
Pathology
Department of Biology
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Frank Mirer, Ph.D. (Principal Reviewer)
Toxicology
International Union, United
Auto Workers
Detroit, Michigan

Robert A. Scala, Ph.D.
Toxicology
Exxon Corporation
East Millstone, New Jersey

Bernard Schwetz, Ph.D., D.V.M.
Toxicology Research Laboratory
Dow Chemical U.S.A.
Midland, Michigan

James Swenberg, Ph.D., D.V.M.
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Stan D. Vesselinovitch, D.V.Sc.*
Departments of Radiology and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D.
Pharmacology
University of Kentucky
College of Medicine
Lexington, Kentucky

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*Unable to attend June 16, 1982 meeting

SUMMARY OF PEER REVIEW COMMENTS

On June 16, 1982 this carcinogenesis bioassay technical report on diallyl phthalate underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Breslow, a principal reviewer for the report on the bioassay of diallyl phthalate, commented that the interpretation of this bioassay is complicated because (1) results are currently available on only a single test species, (2) the MTD may not have been achieved, and (3) benign neoplasms were produced at an unusual anatomic site and appear related to compound administration. Dr. Breslow said that since benign neoplasms of the forestomach were produced at dosages which were apparently well tolerated otherwise, this bioassay provides some evidence for the carcinogenicity of diallyl phthalate in B6C3F$_1$ mice. He said the discussion would be enhanced by including information on compounds besides allyl isothiocyanate which produce neoplasms of the mouse forestomach and by further considering the extent to which papillomas could or should be considered as precursors to frank carcinomas.

As a second principal reviewer, Dr. Mirer said the proof for concluding the absence of carcinogenicity depends on the weight given to the observation of squamous cell papillomas of the forestomach in male and female mice. The historical incidence of inflammation in control mice not subjected to gavage could assist further in the interpretation of these findings. He thought that the statistical criteria for biological significance had been met and that the NTP should decide whether an increase in these papillomas was evidence of carcinogenicity, based on the pathologist's evaluation of the nature of this tumor. With regard to the equivocal nature of hematopoietic tumors (lymphomas) in male mice, Dr. Mirer noted that among a series of phthalic acid esters and related compounds, there were statistically significant increases in hematopoietic tumors only for dimethylterephthalate. Finally, he concluded it would have been helpful to have the bioassay results in rats to aid in interpreting the significance of the borderline findings in mice.

As third principal reviewer, Dr. Holland had several comments regarding conjectures about mode of metabolism, site of metabolism, and major metabolites of diallyl phthalate. He said that since there was no pathological evidence given for hepatocellular necrosis in prechronic studies, some of the conjecture relating to certain metabolites causing this lesion were speculative. He agreed with the conclusions. He questioned the absence of pathologic findings in mice that died during the 13-week study. His concern was that too low a dose might have been chosen for the chronic study as a result of a gavage error in mice killed at 400 mg/kg. Dr. Swenberg commented that the dose-related increase in forestomach lesions may have been a better indicator than decreased body weight gain that an MTD was achieved in this study.

Dr. W. Kluwe, NTP, said there were significant differences observed for the forestomach lesions in dosed mice only when compared with historical controls, and then only marginally. Thus, the effects were probably compound-related, but were not clear evidence of a carcinogenic response. He indicated that there were no significant lesions in the prechronic study.

In further discussion, Dr. Highland argued that the evidence presented for forestomach lesions along with the likely (if hypothetical) metabolism of diallyl phthalate leads to a conclusion that suggests a carcinogenic effect. Dr. Breslow said he had problems with saying there was a dose-related increase in papillomas, while on the other hand this increase had nothing to do with carcinogenicity. Dr. Kluwe agreed and said that development of inflammation and hyperplasia of the forestomach was clearly compound related, while the papillomas may have been compound related. He said this distinction would be made in the conclusion. Dr. Breslow stated that the papillomas could well have been produced by a local toxic reaction and, in any event, were only equivocally related to compound administration.

Dr. Breslow then moved that the technical report on the bioassay of diallyl phthalate be accepted with the revisions indicated. Dr. Holland seconded the motion, and the report was approved by the Peer Review Panel (nine affirmative votes with one abstention, Dr. Highland).

I. INTRODUCTION

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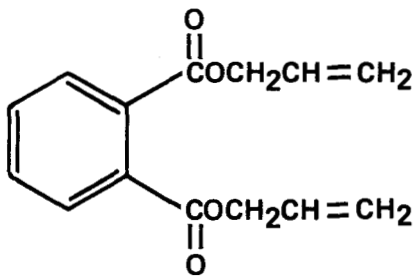


DIALLYL PHTHALATE

CAS NO. 131-17-9
$C_{14}H_{14}O_4$ Mol. Wt. 246.24

Diallyl phthalate is a widely used crosslinking agent for unsaturated polyesters. Diallyl phthalate or diallyl phthalate polyester blends are used primarily as plasticizers and carriers for adding catalysts and pigments to polyesters and in molding, electrical parts, laminating compounds, and impregnation of metal castings (Modern Plastics Encyclopedia, 1979; Kirk-Othmer, 1979). Rubber compounds, epoxy formulations, and polyurethane foams may also contain diallyl phthalate. Annual production of diallyl phthalate in the United States exceeds 5,000 pounds (USITC, 1980); precise figures are not available.

The pharmacokinetics of diallyl phthalate have not been studied extensively. Other dialkyl phthalate esters, however, appear to be easily hydrolyzed to their corresponding alcohols and monoalkyl phthalates (Carter et al., 1974; Rowland, 1974), possibly in the gut prior to intestinal absorption (Albro and Thomas, 1973; Rowland, 1974; Rowland et al., 1977). Consequently, the parent compound was not isolated from the tissues of rats 4 hours after oral administration of near-lethal amounts of diallyl phthalate (Carter et al., 1978).

A single metabolite, 3-hydroxypropylmercapturic acid, has been isolated from the urine of rats administered diallyl phthalate (Kaye and Young, 1972). Since allyl alcohol and acrolein (allyl aldehyde, 2-propenal) are also excreted as 3-hydroxypropylmercapturic acid in the urine of rats, it has been hypothesized that one or both ester linkages of diallyl phthalate are initially hydrolyzed and that the released allyl alcohol is then oxidized to acrolein (Kaye and Young, 1972; Kaye, 1973). Acrolein reacts with glutathione (2-aldehydoethylglutathione) and is then reduced to an alcohol and excreted as the N-acetylcysteine conjugate (mercapturic acid). The proposed metabolism of diallyl phthalate is illustrated in Figure 1. Conjugation of acrolein with glutathione occurs in the liver *in vivo* (Giles, 1979), but has not been demonstrated in other tissues.

Patel et al. (1980) demonstrated the ability of liver tissue from phenobarbital-pretreated rats to metabolize allyl alcohol to acrolein and allylic acid (2-propenoic acid). The characteristics of the oxidation of allyl alcohol to acrolein were consistent with catalysis by alcohol dehydrogenase, while those of oxidation of acrolein to allylic acid were consistent with catalysis by aldehyde dehydrogenase. Allyl alcohol and acrolein were also shown to undergo hepatic microsomal oxidation to the epoxides glycidol and glycidaldehyde (Patel et al., 1980). These epoxides were subsequently hydrolyzed to diols (glycerol, glyceraldehyde) or conjugated with glutathione. The products of the latter reaction were not isolated or identified.

The conjugation of the reactive aldehyde acrolein with glutathione occurs *in vitro* in the absence of enzyme mediation (Giles, 1979), but may be catalyzed by glutathione transferases *in vivo*. Conjugation of an allyl alcohol metabolite with glutathione would appear to be a detoxication reaction, since Hanson and Anders (1978) have reported that diethyl maleate-induced depletion of glutathione enhanced the lethal potency of allyl alcohol in rats.

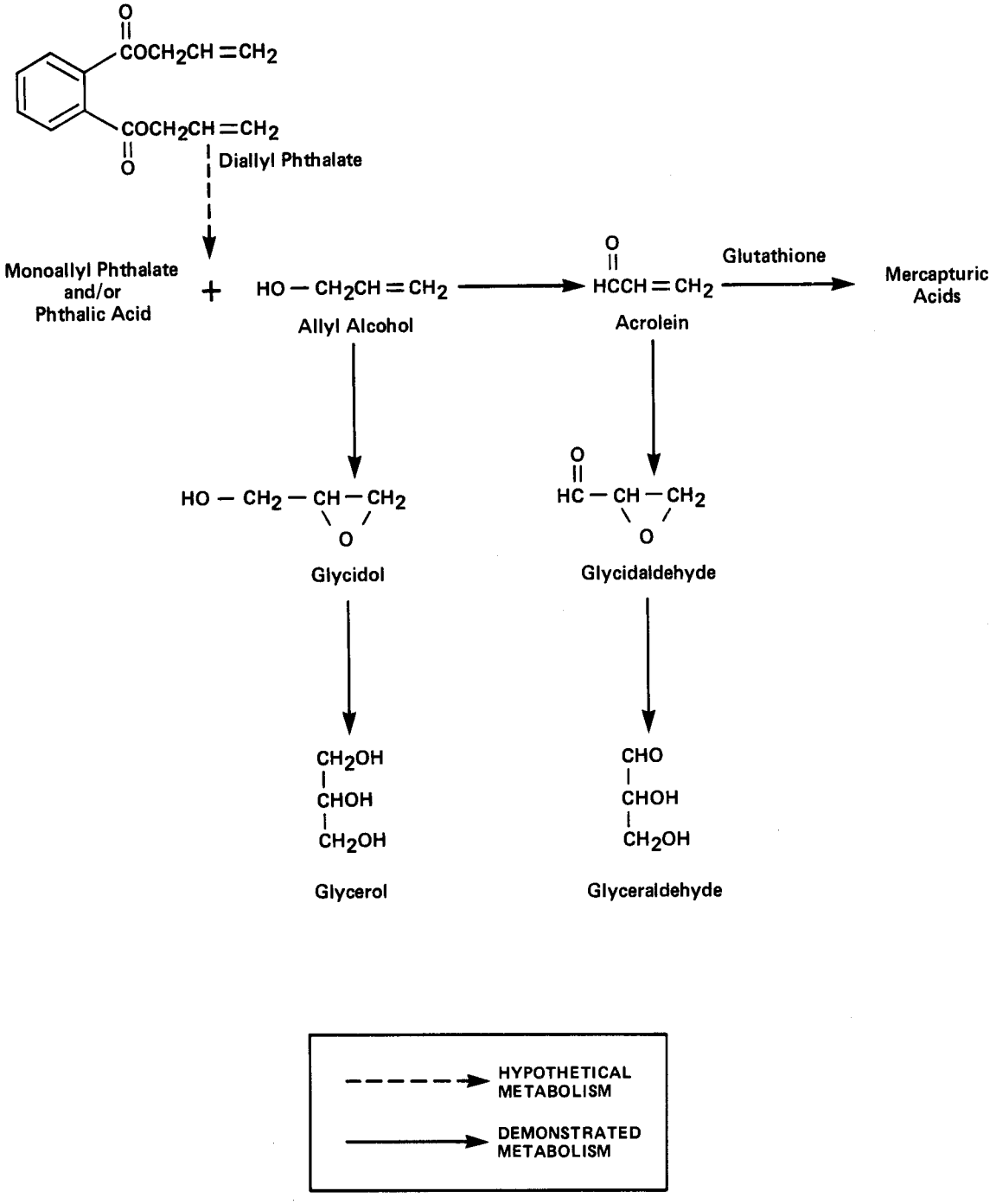


Figure 1. Metabolism of Diallyl Phthalate

I. INTRODUCTION

Oral LD_{50} values of 0.77 to 1.7 g/kg diallyl phthalate have been reported in rats of unspecified strain and sex (Hagan et al., 1949; Peakall, 1975; Carter et al., 1978). The major toxic effect in rats of the purported diallyl phthalate metabolite allyl alcohol is periportal hepatocellular necrosis, a lesion believed to be caused by acrolein, the product of allyl alcohol oxidation (Rees and Tarlow, 1967; Reid, 1972). The hepatotoxic effects of allyl alcohol in rats regress despite continued administration, suggesting adaptation of the liver to the presence of allyl alcohol or acrolein (Butterworth et al., 1978; Lake et al., 1978). The mechanism of the developed resistance to allyl alcohol is not known.

Diallyl phthalate was not mutagenic to *Salmonella typhimurium* in either the presence or the absence of a 9,000 xg supernatant fraction from the liver of Aroclor 1254-treated rats (NTP, 1982d). However, allyl alcohol was shown to be weakly mutagenic to *S. typhimurium* TA 1535 in the presence of a 9,000 xg supernatant fraction from Aroclor 1254-treated hamster (not rat) liver, and acrolein was demonstrated to be a direct-acting mutagen to *S. typhimurium* TA 98 (Lijinsky and Andrews, 1980). The mutagenicity of acrolein to *S. typhimurium* has been confirmed by a second laboratory (NTP, 1980), but acrolein failed to induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (NTP, 1982e). The allyl alcohol metabolites glycidol and glycidaldehyde are direct-acting mutagens to *S. typhimurium* (McCann et al., 1979). There is considerable evidence, therefore, of genotoxic effects of purported diallyl phthalate metabolites, but not of the parent compound.

Lifetime carcinogenicity studies of diallyl phthalate in Fisher 344/N rats* and of acrolein in Fisher 344 rats are currently in progress (IARC, 1978). Inhalation by hamsters of the respiratory tract irritant acrolein at 4 ppm for 1 year or at 10 ppm throughout life (5 days per week) failed to cause an increase in tumors of the respiratory tract (Personal Communication, Dr. P. Nettesheim, National Institute of Environmental Health Sciences; Feron and Kruysse, 1977). No information is currently available concerning the carcinogenic effect of acrolein on non-respiratory tract tissues or the effects of oral administration. Glycidaldehyde was reported to cause both benign and malignant tumors of the skin when applied dermally to female mice throughout their lifetime (Van Duuren et al., 1965). There is limited evidence, therefore, for the carcinogenicity of one possible diallyl phthalate metabolite (glycidaldehyde), while the carcinogenic potential of another purported metabolite (acrolein) is currently under study.

Diallyl phthalate was tested in the Bioassay Program because of its widespread use and potential for human exposure and because of the lack of prior chronic toxicity testing.

*The NTP carcinogenesis bioassay of diallyl phthalate in rats was completed in February 1982, and is currently being evaluated..

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

PREPARATION OF DOSES

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDIES

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

Diallyl phthalate was obtained in a single batch (Lot No. 25-121) from Hardwicke Chemical Company (Elgin, SC). Purity and identity analyses were conducted at Midwest Research Institute (MRI). Results of elemental analyses were consistent with theoretical values. Only a single component was detected by thin-layer chromatography. Eight impurities (comprising a total of approximately 1% of the area of the major peak) were detected by gas-liquid chromatography. Infrared and nuclear magnetic resonance spectra were consistent with those in the literature (Appendix C). Diallyl phthalate was found to be stable for 15 days at room temperature and in the presence of light, but it was stored in the dark at 4°C throughout the bioassay. No change in the purity of the bulk chemical supply was observed throughout the study when periodically analyzed by gas-liquid chromatography and infrared spectroscopy.

PREPARATION OF DOSES

Diallyl phthalate and corn oil were mixed to produce the desired concentrations. Dose preparation and storage time and conditions are summarized in Table 1 for each test phase. Diallyl phthalate in corn oil was found to be stable for two weeks at 25°C (Appendix D). Randomly selected samples of diallyl phthalate/corn oil mixtures were analyzed periodically (Appendix E). The results from analysis of chemical/vehicle mixtures at Litton Bionetics and at MRI indicate that all of the formulations were satisfactorily prepared.

SHORT-TERM STUDIES

Single-Dose Study

Male and female B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD) 6 weeks before the test began. Animals were approximately 10 weeks old when placed on study. Details of animal maintenance are presented in Table 1.

Diallyl phthalate in corn oil was administered by gavage to groups of five male mice in single doses of 681, 1,000, 1,470, or 2,150 mg/kg and to groups of five female mice in single doses of 1,000, 1,470, 2,150, or 3,160 mg/kg. All animals were observed for mortality every 30 minutes on the day of dosing and then daily for the next 13 days. Weights were measured on the day of dosing and on days 7 and 14, postdosing. Necropsies were performed on all animals.

Fourteen-Day Study

Male and female B6C3F$_1$ mice were obtained from Frederick Cancer Research Center 3 weeks before the study began. Animals were approximately 7 weeks old when placed on study.

Groups of five males and five females received 0, 50, 100, 200, 400, or 600 mg/kg diallyl phthalate in corn oil by gavage for 14 consecutive days. Animals were housed five per cage and received water and feed *ad libitum*.

Details of animal maintenance are presented in Table 1. The mice were observed daily for mortality and weighed weekly. Necropsies were performed on all animals.

Thirteen-Week Study

Thirteen-week studies were conducted to evaluate the cumulative nature of diallyl phthalate toxicity and to determine the doses to be used in the chronic studies.

Four-week-old male and female B6C3F$_1$ mice were obtained from the Frederick Cancer Research Center 4 weeks before being assigned to cages and dose groups. The animals were approximately 8 weeks old when placed on study. Mice were housed five per cage in polycarbonate cages covered with nonwoven filter sheets (Table 1). Racks and filters were replaced every two weeks. Cages, bedding, and water bottles were replaced twice per week. Feed and tap water (acidified

with hydrochloric acid to pH 2.5 for bacterial control) were available *ad libitum*.

Diallyl phthalate was administered to groups of 10 mice of each sex at doses of 0, 25, 50, 100, 200, or 400 mg/kg in corn oil by gavage, five times per week for 13 weeks. Animals were checked for mortality and signs of morbidity twice daily Monday through Friday and once per day on weekends. Each animal was given a weekly clinical examination, including palpation for tissue masses or swelling. Body weights were measured weekly.

Animals judged to be moribund and those surviving to the end of the study were killed with carbon dioxide. Necropsies were performed on all animals not excessively autolyzed or cannibalized. The following tissues were examined microscopically in control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Study Design

Groups of 50 mice of each sex received 0 (vehicle control), 150, or 300 mg/kg diallyl phthalate in corn oil by gavage, 5 days per week, for 103 weeks.

Source and Specifications of Test Animals

Four-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, and assigned to cages according to a table of random numbers. Another table of random numbers was used to assign cages to control and dosed groups. All animals were approximately 7 weeks old when placed on study.

A quality control skin grafting program to monitor genetic integrity of inbred mice used to produce the hybrid $B6C3F_1$ test animal has been in effect since early 1978. In mid-1981, data were obtained showing incompatibility between the NIH C3H reference colony and the C3H colony from a Bioassay Program supplier. In August, 1981, inbred parental lines of mice were further tested for genetic homogeneity via isozyme and protein electrophoregrams which demonstrate phenotypic expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of random bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in this bioassay. The influence of the potential genetic non-uniformity in the hybrid mice on the bioassay results is not known. However, the bioassay is valid since matched, concurrent controls were included in the study.

Animal Maintenance

Mice were housed five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were changed once every two weeks. Cages, bedding, and glass water bottles (equipped with stainless steel sipper tubes) were replaced twice per week. Feed and tap water (acidified to pH 2.5 for bacterial control) were available *ad libitum*. Stainless steel feed containers were changed once per week.

The temperature in the animal room was 22°-24°C and the humidity was 30%-70%. Room air was changed 12 to 15 times per hour. Fluorescent lighting provided illumination 12 hours per day. No other chemicals were on test in the room.

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity or mortality. Clinical signs were recorded monthly. Individual animals were weighed

weekly for the first 13 weeks, then monthly to week 93, and every 2 weeks thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissues masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder, pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

Necropsies were performed on all animals not excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically is not necessarily equal to the number of animals that were placed on study in each group.

Neoplastic nodules were classified according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechniques were evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10 percent of the animals were evaluated by an experienced rodent pathologist. Slides of all target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG's experienced rodent pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described, in part, by Ward et al., 1978.) The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al. 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which that site was examined microscopically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to microscopic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high-and low-dose groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point

in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. The computational details of both methods are presented in Peto et al. (1980).

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose Study	14-Day Study	13-Week Study	2-Year Study
Experimental Design				
Size of Test Groups	5 males and 5 females	5 males and 5 females	10 males and 10 females	50 males and 50 females
Doses	Males: 681, 1,000, 1,470, or 2,150 mg/kg body weight diallyl phthalate in corn oil Females: 1,000, 1,470, 2,150, or 3,160 mg/kg body weight diallyl phthalate in corn oil	0, 50, 100, 200, 400, or 600 mg/kg body weight diallyl phthalate in corn oil, based on group mean weights	0, 25, 50, 100, 200, or 400 mg/kg body weight diallyl phthalate in A&P brand corn oil; each animal received 3.3 ml/kg body weight of dose solution, based on group mean weights	0, 150, or 300 mg/kg body weight diallyl phthalate in A&P brand corn oil; each animal received 10 ml/kg body weight of dose solution, based on group mean weights
Duration of Dosing	Single dose	Daily for 14 days	Five days per week for 13 weeks	Five days per week for 103 weeks
Type and Frequency of Observation	Observed for mortality every 1/2 hour on day of testing and daily thereafter	Observed daily for mortality; weighed on days 0, 7, and 14	Observed twice daily on weekdays and once a day on weekends for mortality and morbidity; weighed weekly	Observed twice daily for mortality and morbidity; weighed at least once per month
Necropsy and Histological Examination	Necropsies were performed on all animals	Necropsies were performed on all animals	Necropsies and histologic examinations were performed on control and high-dose groups	Necropsies and histologic examinations were performed on all animals
Animals and Animal Maintenance				
Species	B6C3F$_1$ mice	B6C3F$_1$ mice	B6C3F$_1$ mice	B6C3F$_1$ mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Same as single-dose study	Same as single-dose study	Charles River Breeding Laboratories (Portage, MI)
Time Held Before Start of Test	6 weeks	3 weeks	4 weeks	3 weeks
Age When Placed on Study	10 weeks	7 weeks	8 weeks	7 weeks
Age When Killed	12 weeks	9 weeks	21 weeks	113 weeks
Method of Animal Distribution			Randomized by weight	Assigned to cages according to a table of random numbers and to groups according to another table of random numbers

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Study	14-Day Study	13-Week Study	2-Year Study
Feed	Purina® Laboratory Chow Ralston Purina Co. (St. Louis, MO)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Bedding	Ab-sorb-dri® wood chips Lab Products, Inc. (Garfield, NJ)	Same as single-dose study	Same as single-dose study	Same as single-dose study; changed twice weekly
Water	Tap water acidified with HCl (pH 2.5) available in bottles	Same as single-dose study	Same as single-dose study; bottles changed twice weekly	Same as single-dose study; bottles changed twice weekly
Cages	Polycarbonate	Same as single-dose study	Polycarbonate shoe-box type hanging cage; cages changed twice weekly	Polycarbonate Lab Products Inc. (Garfield, NJ) and Hazleton Systems (Aberdeen, MD); cages changed twice weekly
Cage Filters	Non-woven polyester filter sheets, Snow Filtration Co., Cincinnati, OH	Same as single-dose study	Same as single-dose study	Same as single-dose study
Animals per Cage	Five	Five	Five	Five
Animal-Room Environment				22°-24°C; 30%-70% relative humidity; room air changed 12-15 times per hour; 12 hours of fluorescent light per day
Other Chemicals on Test in the Same Room	—	None	None	None
Chemical Vehicle Mixture Preparation	Diallyl phthalate was dissolved in corn oil at a concentration of 200 mg/ml	Diallyl phthalate was dissolved in corn oil at a concentration of 50 mg/ml	Appropriate amounts of diallyl phthalate and corn oil were mixed to give the desired concentrations	Appropriate volumes of of diallyl phthalate and corn oil were mixed to give the desired concentrations
Maximum Storage Time	Prepared within 2 hours of dosing	Same as single-dose study	Same as single-dose study	1 week
Storage Conditions	—	—	—	Room temperature

III. RESULTS

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SHORT-TERM STUDIES

Single-Dose Study

All males and females that received 2,150 mg/kg and all females that received 3,160 mg/kg died. At least one death occurred in all of the other dosed groups, except for females that received 1,000 mg/kg (Table 2). No chemically-related lesions were observed at necropsy.

Fourteen-Day Study

Deaths occurred in groups of mice receiving 400 or 600 mg/kg diallyl phthalate but not in groups receiving lower doses. Mean body weight gains of dosed mice were not depressed relative to controls (Table 3). No chemically-related lesions were observed at necropsy.

Thirteen-Week Study

A single death occurred in male mice in the 400 mg/kg group and in female mice in the 0, 25, 50, 200, and 400 mg/kg groups (Table 4). Three of these six deaths were unequivocally caused by accidents; the other three animals did not exhibit pathologic lesions that were clearly compound related. None of the deaths, therefore, were considered to be chemically induced. Mean body weight gain in male mice administered 400 mg/kg was depressed 12% relative to controls, but the variabilities in body weight gain amongst groups and the small absolute change over the 13-week period suggest that the perceived difference was of little or no toxicological significance. Neither gross nor microscopic alterations related to chemical administration were observed in any of the high-dose mice.

Doses of 150 and 300 mg/kg diallyl phthalate were selected for the chronic test because of deaths in the 14-day study at 400 and 600 mg/kg, although neither deaths nor pathologic lesions related to chemical administration were produced by 400 mg/kg diallyl phthalate in the 13-week study.

TABLE 2. SURVIVAL OF MICE ADMINISTERED A SINGLE DOSE OF DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Males		Females	
	Survival *(a)*	(Day of Death)	Survival *(a)*	(Day of Death)
681	4/5	(1)	*(b)*	
1,000	3/5	(1,2)	5/5	
1,470	1/5	(1,1,1,1)	4/5	(1)
2,150	0/5	(2,2,3,3,3)	0/5	(1,1,1,1,2)
3,160	*(b)*		0/5	(2,2,2,2,2)

(a) Number surviving/number initially in group
(b) Not tested at this dose

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival (*a*) (Day of Death)	Mean Body Weights (grams)			Final Body Weight Relative to Controls (*b*) (Percent)
		Initial	Final	Change	
MALES					
0	5/5	21	23	+2	
50	5/5	21	23	+2	0
100	5/5	21	23	+2	0
200	5/5	21	24	+3	+ 4
400	4/5(10)	21	24	+3	+ 4
600	3/5(3,4)	21	23	+2	0
FEMALES					
0	5/5	17	18	+1	
50	5/5	17	18	+1	0
100	5/5	17	19	+2	+ 6
200	5/5	17	19	+2	+ 6
400	3/5(3,3)	17	19	+2	+ 6
600	2/5(3,3,3)	17	21	+4	+17

(*a*) Number surviving/number per group

(*b*) Weight of the dosed group relative to that of the controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival (*a*) (Week of Death)	Mean Body Weights (grams)			Final Body Weight Relative to Controls (*b*) (Percent)
		Initial	Final	Change	
MALES					
0	10/10	23.6	27.8	+ 4.2	
25	10/10	22.9	27.9	+ 5.0	+10
50	10/10	23.1	28.1	+ 5.0	0
100	10/10	23.3	28.5	+ 5.2	+ 3
200	10/10	23.6	27.6	+ 4.0	- 1
400	9/10 (12)	23.2	26.9	+ 3.7	- 3
FEMALES					
0	9/10 (3)	17.4	21.4	+ 4.0	
25	9/10 (1, *c*)	17.4	21.1	+ 3.7	- 1
50	9/10 (1, *c*)	17.5	21.8	+ 4.3	+ 2
100	10/10	17.4	21.2	+ 3.8	- 1
200	9/10 (2, *c*)	17.4	21.8	+ 4.4	+ 2
400	9/10 (1)	17.4	21.9	+ 4.5	+ 2

(*a*) Number surviving/number per group

(*b*) Weight of the dosed group relative to that of the controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

(*c*) Accidental death

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control animals were practically indistinguishable throughout the study (Figure 2 and Appendix F, Table F1). Chemically-induced clinical signs of morbidity were not observed at any time.

Survival

Estimates of the probabilities of survival of male and female mice administered diallyl phthalate, and those of the controls, are shown by the Kaplan and Meier curves in Figure 3. No significant differences in survival were observed between dosed and control groups.

Among male mice, 38/50 (76%) of the controls, 38/50 (76%) of the low-dose, and 32/50 (64%) of the high-dose group lived to the end of the study at 106 weeks. In female mice, 38/50 (76%) of the controls, 35/50 (70%) of the low-dose, and 39/50 (78%) of the high-dose group lived to the end of the study at 106 weeks. These incidences include two high-dose males, one control female, and two low-dose females that died during the final week of the study (after cessation of chemical administration); for statistical purposes, these animals were considered to have been killed at the end of the study.

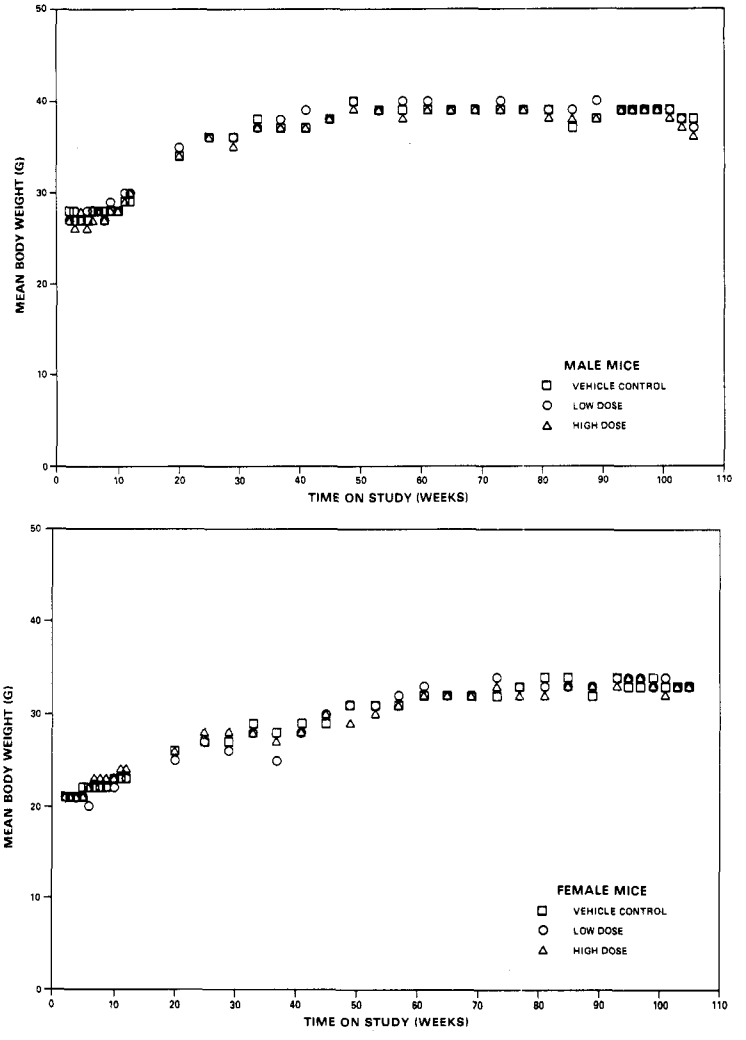
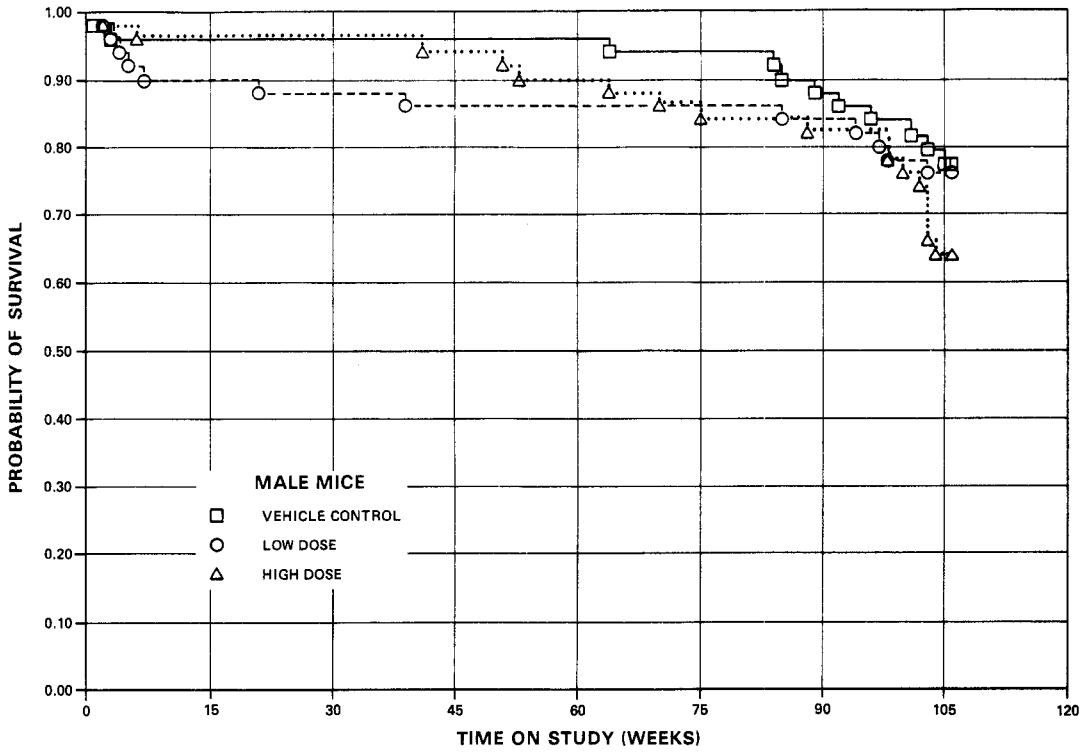


Figure 2. Growth Curves for Mice Administered Diallyl Phthalate in Corn Oil by Gavage



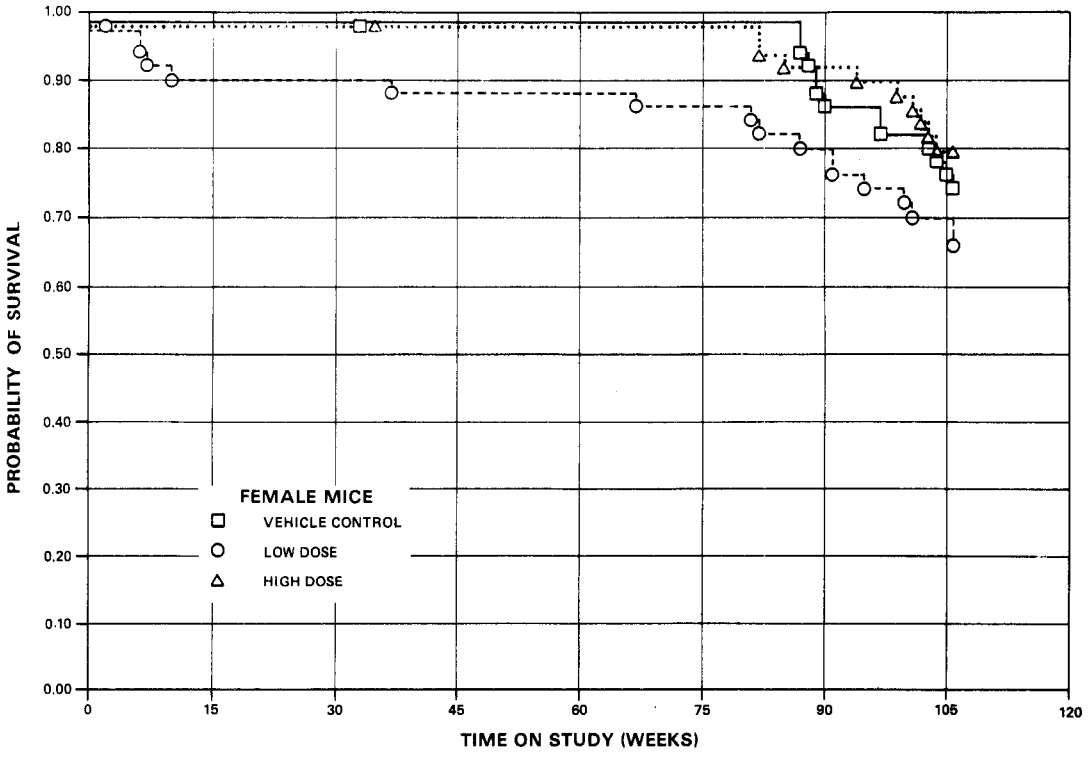


Figure 3. Survival Curves for Mice Administered Diallyl Phthalate in Corn Oil by Gavage

Pathology and Statistical Analyses of Results

Histopathologic characterizations of the neoplasms detected in mice are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 show the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Lesions of the forestomach are summarized in Tables 5 and 6 and Appendix B, Tables B1 and B2. Tables 7 and 8 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Hematopoietic System: Statistically significant positive trends ($P<0.05$, life table and incidental tumor tests) were observed in the incidence of male mice with lymphomas (overall rates of 12%, 10%, and 24% in control, low-, and high-dose groups) and in the combined incidence of male mice with lymphomas or leukemias (overall rates of 12%, 12%, and 24% in control, low-, and high-dose groups). No significant differences were observed, however, in pairwise comparisons between incidences in male control and dosed groups. The incidences of female mice with hematopoietic system tumors were not statistically significant.

Liver: Statistically significant ($P<0.05$) positive trends were observed in the incidences of male mice with hepatocellular adenomas (overall rates of 0%, 0%, and 6% in control, low-, and high-dose groups). No significant differences, however, were observed in pairwise comparisons between control and dosed groups of male mice, nor was the incidence of hepatocellular adenomas or carcinomas increased significantly in male or female mice.

Uterus: Statistically significant ($P<0.05$) negative trends were observed in the incidences of female mice with endometrial stromal polyps (overall rates of 8%, 4%, and 0% in control, low-, and high-dose groups). No significant differences, however, were observed in pairwise comparisons between control and dosed groups of female mice.

Forestomach: The incidences of dosed male and female mice with papillomas, hyperplasia, or inflammatory lesions were increased relative to those for the controls (Table 5). The papillomas consisted of frond-like proliferations of squamous cells supported by a stalk of fibrovascular stroma. Hyperplasia consisted of more diffuse squamous cell proliferations, with no stalk formation and minimal protrusion into the gastric lumen. Hyperplasia often was associated with chronic inflammation of the underlying submucosa and surrounding mucosa. Chronic inflammation of the forestomach also was observed as a separate entity.

The incidences of both male and female mice with papillomas of the forestomach were 0%, 2%, and 4% for control, low-, and high-dose groups, respectively (Table 5). All papillomas were diagnosed at terminal kill, producing incidences of 0/38 (0%), 1/38 (3%), 2/32 (6%) and 0/38 (0%), 1/35 (3%), and 2/39 (5%) in control, low-, and high-dose male and female mice, respectively. Statistical comparisons with concurrent controls are performed only when overall incidences of 5% or more are observed, because of the insensitivity of the statistical tests for detecting effects at low incidences with the limited number of animals utilized in a chronic bioassay. Comparisons with historical controls are described in Chapter IV (Discussion and Conclusions).

Of the six mice with forestomach papillomas, the one male mouse and the one female mouse from the low-dose group, and one of the two female mice from the high-dose group had neither forestomach hyperplasia nor chronic forestomach inflammation. One of the two male mice with forestomach papillomas from the high-dose group also had forestomach hyperplasia, while the other exhibited chronic forestomach inflammation. The remaining female mouse with forestomach papillomas in the high-dose group had both chronic inflammation and hyperplasia of the forestomach. A correlation between papillomas and inflammation or hyperplasia could not be proved because of the low incidence of forestomach papillomas. Hyperplasia occurred more frequently in mice with chronic forestomach inflammation than in those without inflammation in both the low- and high-dose male groups and in the control and high-dose female groups (Table 6).

TABLE 5. INCIDENCES OF MICE WITH LESIONS OF THE FORESTOMACH *(a)*

	Males			Females		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
No. of Mice Examined	49	47	49	48	47	49
Papilloma	0	1	2	0	1	2
Hyperplasia	0	7*(b)*	9*(b)*	4	1	14*(b)*
Inflammation, Chronic	0	4	8*(b)*	2	1	9*(c)*
Inflammation, Suppurative	1	0	1	0	0	2
Ulcer	0	2	1	1	1	0
Erosion	0	0	1	0	0	0

(a) The number of animals exhibiting the lesions is shown.
(b) Significantly greater than control (by Fisher's exact test), $P<0.01$.
(c) Significantly greater than control (by Fisher's exact test), $P<0.05$.

TABLE 6. COMPARATIVE INCIDENCES OF FORESTOMACH HYPERPLASIA AND CHRONIC INFLAMMATION OF THE FORESTOMACH IN MICE

Sex	Chronic Inflammation	Incidence of Hyperplasia (%)		
		Control	Low Dose	High Dose
Male	Present	0/0 (0%)	3/4 (75%)*(a)*	5/8 (62%)*(b)*
	Absent	0/49 (0%)	4/43 (9%)	4/41 (10%)
Female	Present	2/2 (100%)*(a)*	0/1 (0%)	9/9 (100%)*(c)*
	Absent	2/46 (4%)	1/46 (2%)	5/40 (12%)

(a) Significantly greater incidence of hyperplasia in mice with chronic inflammation (present) than in mice without (absent), $P<0.01$.
(b) Same as a, $P<0.005$.
(c) Same as a, $P<0.001$.

TABLE 7. ANALYSES OF MALE MICE WITH PRIMARY TUMORS *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	3/49 (6%)	5/50 (10%)
Adjusted *(c)*	7.9%	7.6%	14.8%
Terminal *(d)*	3/38 (8%)	2/38 (5%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.218	P=0.662	P=0.274
Incidental Tumor Test	P=0.279	P=0.624	P=0.313
Cochran-Armitage Trend, Fisher Exact Tests	P=0.283	P=0.651	P=0.357
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/50 (10%)	4/49 (8%)	5/50 (10%)
Adjusted *(c)*	12.5%	10.1%	14.8%
Terminal *(d)*	4/38 (11%)	3/38 (8%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.478	P=0.505N	P=0.532
Incidental Tumor Test	P=0.481	P=0.618N	P=0.500
Cochran-Armitage Trend, Fisher Exact Tests	P=0.568	P=0.513N	P=0.630
Hematopoietic System: Lymphoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	5/50 (10%)	12/50 (24%)
Adjusted *(c)*	15.8%	13.2%	32.7%
Terminal *(d)*	6/38 (16%)	5/38 (13%)	8/32 (25%)
Statistical Tests *(e)*			
Life Table	P=0.031	P=0.500N	P=0.051
Incidental Tumor Test	P=0.037	P=0.500N	P=0.058
Cochran-Armitage Trend, Fisher Exact Tests	P=0.063	P=0.500N	P=0.096
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	6/50 (12%)	6/50 (12%)	12/50 (24%)
Adjusted *(c)*	15.8%	15.4%	32.7%
Terminal *(d)*	6/38 (16%)	5/38 (13%)	8/32 (25%)
Statistical Tests *(e)*			
Life Table	P=0.034	P=0.620	P=0.051
Incidental Tumor Test	P=0.045	P=0.608	P=0.058
Cochran-Armitage Trend, Fisher Exact Tests	P=0.067	P=0.620	P=0.096
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted *(c)*	9.4%	2.6%	5.5%
Terminal *(d)*	1/38 (3%)	1/38 (3%)	1/32 (3%)
Statistical Tests *(e)*			
Life Table	P=0.275N	P=0.192N	P=0.380N
Incidental Tumor Test	P=0.238N	P=0.286N	P=0.312N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.238N	P=0.181N	P=0.339N

TABLE 7. ANALYSES OF MALE MICE WITH PRIMARY TUMORS *(a)* (Continued)

	Control	Low Dose	High Dose
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted *(c)*	0.0%	0.0%	9.4%
Terminal *(d)*	0/38 (0%)	0/38 (0%)	3/32 (9%)
Statistical Tests *(e)*			
Life Table	P=0.026	*(f)*	P=0.092
Incidental Tumor Test	P=0.026	*(f)*	P=0.092
Cochran-Armitage Trend, Fisher Exact Tests	P=0.038	*(f)*	P=0.121
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	7/50 (14%)	5/49 (10%)	4/50 (8%)
Adjusted *(c)*	15.5%	12.7%	12.5%
Terminal *(d)*	2/38 (5%)	4/38 (11%)	4/32 (13%)
Statistical Tests *(e)*			
Life Table	P=0.286N	P=0.405N	P=0.347N
Incidental Tumor Test	P=0.233N	P=0.507	P=0.312N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.210N	P=0.394N	P=0.262N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	7/50 (14%)	5/49 (10%)	7/50 (14%)
Adjusted *(c)*	15.5%	12.7%	21.9%
Terminal *(d)*	2/38 (5%)	4/38 (11%)	7/32 (22%)
Statistical Tests *(e)*			
Life Table	P=0.455	P=0.405N	P=0.502
Incidental Tumor Test	P=0.510	P=0.507	P=0.524
Cochran-Armitage Trend, Fisher Exact Tests	P=0.560	P=0.394N	P=0.613

(a) Dosed groups received 150 or 300 mg/kg of diallyl phthalate by gavage.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(f) Not significant; no tumors in low-dose or vehicle control group.

TABLE 8. ANALYSES OF FEMALE MICE WITH PRIMARY TUMORS *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	0/48 (0%)	3/48 (6%)
Adjusted *(c)*	2.6%	0.0%	7.6%
Terminal *(d)*	1/38 (3%)	0/35 (0%)	2/38 (5%)
Statistical Tests *(e)*			
Life Table	P=0.181	P=0.516N	P=0.307
Incidental Tumor Test	P=0.197	P=0.516N	P=0.323
Cochran-Armitage Trend, Fisher Exact Tests	P=0.168	P=0.510N	P=0.293
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	16/50 (32%)	14/50 (28%)	18/49 (37%)
Adjusted *(c)*	36.8%	34.7%	42.3%
Terminal *(d)*	11/38 (29%)	9/35 (26%)	15/39 (38%)
Statistical Tests *(e)*			
Life Table	P=0.406	P=0.536N	P=0.440
Incidental Tumor Test	P=0.292	P=0.543	P=0.331
Cochran-Armitage Trend, Fisher Exact Tests	P=0.348	P=0.414N	P=0.388
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(b)*	2/50(4%)	0/50 (0%)	4/49 (8%)
Adjusted *(c)*	5.1%	0.0%	9.1%
Terminal *(d)*	1/38 (3%)	0/35 (0%)	1/39 (3%)
Statistical Tests *(e)*			
Life Table	P=0.241	P=0.264N	P=0.356
Incidental Tumor Test	P=0.269	P=0.305N	P=0.390
Cochran-Armitage Trend, Fisher Exact Tests	P=0.216	P=0.247N	P=0.329
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	2/49 (4%)	3/49 (6%)
Adjusted *(c)*	2.3%	5.1%	7.7%
Terminal *(d)*	0/38 (0%)	1/35 (3%)	3/39 (8%)
Statistical Tests *(e)*			
Life Table	P=0.234	P=0.467	P=0.316
Incidental Tumor Test	P=0.177	P=0.731	P=0.254
Cochran-Armitage Trend, Fisher Exact Tests	P=0.216	P=0.492	P=0.301
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	4/44 (9%)	7/43 (16%)	8/46 (17%)
Adjusted *(c)*	10.9%	20.9%	21.1%
Terminal *(d)*	3/35 (9%)	6/32 (19%)	8/38 (21%)
Statistical Tests *(e)*			
Life Table	P=0.187	P=0.211	P=0.215
Incidental Tumor Test	P=0.211	P=0.192	P=0.233
Cochran-Armitage Trend, Fisher Exact Tests	P=0.166	P=0.247	P=0.199

TABLE 8. ANALYSES OF FEMALE MICE WITH PRIMARY TUMORS *(a)* (Continued)

	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	4/48 (8%)	2/49 (4%)	0/49 (0%)
Adjusted *(c)*	10.5%	5.7%	0.0%
Terminal *(d)*	4/38 (11%)	2/35 (6%)	0/39 (0%)
Statistical Tests *(e)*			
Life Table	P=0.037N	P=0.375N	P=0.060N
Incidental Tumor Test	P=0.037N	P=0.375N	P=0.060N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.035N	P=0.329N	P=0.056N

(a) Dosed groups received 150 or 300 mg/kg of diallyl phthalate by gavage.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) 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 that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

The doses of diallyl phthalate used in the 2-year study, 150 and 300 mg/kg, were selected because deaths occurred in groups of mice receiving 400 mg/kg or 600 mg/kg diallyl phthalate for 14 days. A dose of 400 mg/kg for 13 weeks, however, produced neither chemically-induced deaths nor pathological lesions and did not cause a clear depression of body weight gain. Since body weight gain and survival in the 2-year study were not different in dosed and control mice and since pathological lesions other than chronic forestomach inflammation, hyperplasia, and papillomas were not observed, a maximally tolerated dose for the purposes of carcinogenicity testing may not have been administered. Numerous deaths at 600 mg/kg in the 14-day study and a marked increase of chronic inflammation of the forestomach in the chronic study, however, indicate that 300 mg/kg, the highest dose in the 2-year study, was at least near a theoretical maximally tolerated dose.

The incidence of male mice with lymphomas and the incidence of male mice with either lymphomas or leukemia were statistically significant ($P< 0.05$) in the trend tests, but not in pairwise comparisons between dosed and control groups. The combined incidence of control male mice with lymphomas or leukemia from this study is within the range for controls at this and other laboratories in the Bioassay Program (Appendix G, Table G2), indicating that the rates in control male mice were not abnormal. A pairwise comparison (using Fisher's exact test) between the incidences in the high-dose group of male mice from this study (12/50, 24%) and the historical rate at Litton Bionetics for control male mice receiving corn oil by gavage (19/120, 16%) is not statistically significant, although a comparison with the overall historical rate from the Bioassay Program (80/661) is statistically significant (P=0.019). Since the incidence of high-dose male mice with either leukemia or lymphoma was not significantly greater than that of concurrent or historical controls at the performing laboratory by pairwise comparisons, this marginal increase was considered only to be equivocally related to diallyl phthalate administration.

The incidence of male mice with hepatocellular adenomas was increased by diallyl phthalate administration, but the data were considered to be of little or no toxicological significance because the incidence in control animals was abnormally low and because the incidences of animals with hepatocellular carcinomas or adenomas or carcinomas (combined) were not increased.

The incidences of both male and female mice with squamous-cell papillomas of the forestomach were greater than those for control $B6C3F_1$ mice in other studies conducted at Litton Bionetics or at other laboratories within the Bioassay Program (Appendix G, Table G1). Because of the low overall tumor incidences (less than 5%), the sample sizes used in this study may have been too small to permit detection of a statistically significant increase in the incidence of a rare tumor type (such as papillomas of the forestomach). Because the historical incidence of this tumor type in control (corn oil-gavaged) mice is generally less than 1%, a pairwise comparison (by Fisher's exact test, one-tailed) was made between the incidences in the high-dose male (2/49) and female (2/49) groups in this study and the historical (corn oil-gavaged) control incidences for male and female mice in the Bioassay Program (Appendix G, Table G1). Statistically significant values were observed (P=0.043, males; P=0.041, females). Therefore, the data in this study are insufficient to indicate that diallyl phthalate caused forestomach papillomas, but results of a comparison of the high incidences of forestomach papillomas in high-dose mice with both concurrent and historical control rates suggest a cause and effect relationship.

The correlation between the occurrence of chronic forestomach inflammation and forestomach hyperplasia (Table 6) suggests that an irritating effect of diallyl phthalate on the gastric epithelium may have predisposed this tissue to the hyperplasia. The incidence of squamous cell papillomas of the forestomach, however, was too low for valid comparisons to be made between their occurrence and the presence of chronic inflammation or hyperplasia. The data are insufficient to indicate whether or not the forestomach papillomas were secondary to the irritation, but the correlation between animals with chemically-induced inflammation and those with hyperplasia supports such a speculation.

Diallyl phthalate has recently completed testing by the National Toxicology Program for carcinogenic effects in Fisher 344/N rats by gavage. Results are currently being evaluated. There are no previous reports available on the carcinogenicity testing of diallyl phthalate. Recent studies conducted by the NTP have demonstrated that di(2-ethylhexyl)phthalate at dietary concentrations of 3,000 to 12,000 ppm is hepatocarcinogenic in rats and mice (NTP, 1982a) and indicate

that butyl benzyl phthalate at dietary concentrations of 12,000 pm may have caused mononuclear-cell leukemia in female rats (NTP, 1982b). The gavage doses of diallyl phthalate used in this study were estimated to be the equivalent of 750 and 1,500 ppm and of 600 and 1,200 ppm for low- and high-dose male and female mice, respectively. Two other chemicals containing allyl groups, allyl chloride and allyl isothiocyanate, were found to produce tumors in standard rodent bioassays when given by gavage (NCI, 1978; NTP, 1982c). Allyl isothiocyanate caused transitional cell tumors of the urinary bladder in male rats, while allyl chloride produced squamous cell carcinomas and papillomas of the forestomach in male and female mice. At least one other allyl compound, therefore, has been shown to produce proliferative lesions of the forestomach similar to those caused by diallyl phthalate. Additional chemicals demonstrated to cause forestomach tumors in the NCI/NTP Carcinogenesis Bioassay Program are shown in Table 9 (Chu et al., 1981).

Allyl compounds can be alkylating agents and direct-acting mutagens, depending on the degree of polarity (electron deficiency, electrophilicity) introduced into the molecule by substituents on the saturated (terminal) carbon atom (Eder et al., 1980). Allyl methanesulfonate, for example, is a strong alkylating agent because of the electronegativity of the methane sulfonate group, whereas allyl isothiocyanate is a very weak alkylating agent. By this criterion (electrophilicity), allyl alcohol would be expected to be only a very weak direct alkylating agent. The limited data available, however, suggest that diallyl phthalate may be metabolized to the electrophile acrolein and to the epoxides glycidol and glycidaldehyde. Studies on the carcinogenic potential of acrolein are currently in progress (IARC, 1978), and Van Duuren et al. (1965) have reported that glycidaldehyde is carcinogenic in mice. Experimentation to determine the extent, dose-dependency, and species-dependency of the metabolism of diallyl phthalate to allyl alcohol, acrolein, and epoxides may provide additional insight into the carcinogenic potential of this compound. Such studies are planned by the NTP.

TABLE 9. CHEMICALS THAT CAUSED FORESTOMACH TUMORS IN THE NCI CARCINOGENESIS BIOASSAY PROGRAM *(a)*

Chemical	Strain/Species	Route of Exposure
1,2-Dibromo-3-chloropropane	Osborne-Mendel rat	Gavage
	$B6C3F_1$ mouse	Gavage
1,2-Dibromoethane	Osborne-Mendel rat	Gavage
	$B6C3F_1$ mouse	Gavage
3-(Chloromethyl)pyridine ·HCl	Fischer 344 rat	Gavage
	$B6C3F_1$ mouse	Gavage
Tris(2,3-dibromopropyl)phosphate	$B6C3F_1$ mouse	Feed
Estradiol mustard	$B6C3F_1$ mouse	Gavage
1,2-Dichloroethane	Osborne-Mendel rat	Gavage
Pivalolactone	Fischer 344/N rat	Gavage
Sulfallate	Osborne-Mendel rat	Feed
4-Chloro-o-phenylenediamine	Fischer 344/N rat	Feed
Cupferron	Fischer 344/N rat	Feed

(a) Data derived from Chu et al. (1981).

IV. DISCUSSION AND CONCLUSIONS

Conclusions: Under the conditions of this bioassay, the development of chronic inflammation and hyperplasia of the forestomach in both male and female B6C3F1 mice was considered to be related to the administration of diallyl phthalate. The development of squamous cell papillomas of the forestomach may also have been related to chemical administration, but the available data are insufficient to indicate a clear cause and effect relationship. An increase in the incidence of male mice with lymphomas was observed, but this increase was considered only to be equivocally related to diallyl phthalate administration. The results of this bioassay, therefore, do not indicate that diallyl phthalate is carcinogenic in B6C3F1 mice, although a maximally tolerated dose may not have been achieved. A carcinogenicity study by the National Toxicology Program of diallyl phthalate in male and female Fischer 344/N rats, employing daily gavage doses of 0 (vehicle control), 50, or 100 mg/kg body weight, is currently being evaluated.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	1 (2%)
LEIOMYOSARCOMA			2 (4%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	3 (6%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	5 (10%)	4 (8%)	11 (22%)
LEUKEMIA,NOS		1 (2%)	
#SPLEEN	(49)	(48)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MESENTERIC L. NODE	(43)	(29)	(41)
MALIGNANT LYMPHOMA, NOS		1 (3%)	1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		1 (2%)
#SPLEEN	(49)	(48)	(50)
HEMANGIOSARCOMA		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA	3 (6%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA			3 (6%)
HEPATOCELLULAR CARCINOMA	7 (14%)	5 (10%)	4 (8%)
#FORESTOMACH	(49)	(47)	(49)
PAPILLOMA, NOS		1 (2%)	2 (4%)
URINARY SYSTEM			
#URINARY BLADDER	(49)	(47)	(49)
ADENOMATOUS POLYP, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(42)
ADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(50)	(48)	(47)
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(49)	(42)	(46)
FOLLICULAR-CELL ADENOMA	2 (4%)	1 (2%)	
#PANCREATIC ISLETS	(49)	(48)	(49)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS		2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEIOMYOSARCOMA, METASTATIC			2 (4%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	9	8	15
MORIBUND SACRIFICE	2	4	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		2
TERMINAL SACRIFICE	38	38	30
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	23	26
TOTAL PRIMARY TUMORS	29	25	34
TOTAL ANIMALS WITH BENIGN TUMORS	8	10	9
TOTAL BENIGN TUMORS	9	11	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	14	19
TOTAL MALIGNANT TUMORS	20	14	21
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(49)
OSTEOSARCOMA		1 (2%)	
NEUROFIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	15 (30%)	12 (24%)	15 (31%)
*MEDIASTINUM	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
*HEMATOPOIETIC SYSTEM	(50)	(50)	(49)
NEOPLASM, NOS	3 (6%)		
#SPLEEN	(47)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	3 (6%)
#LYMPH NODE	(41)	(41)	(40)
LEUKEMIA,NOS	1 (2%)		
#THYMUS	(40)	(36)	(37)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(47)	(49)	(48)
HEMANGIOSARCOMA	1 (2%)		2 (4%)
#LIVER	(50)	(49)	(49)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(48)	(49)	(49)
HEMANGIOMA	1 (2%)		1 (2%)
HEMANGIOSARCOMA			1 (2%)
LYMPHANGIOMA		1 (2%)	
#OVARY	(45)	(45)	(49)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
HEPATOCELLULAR ADENOMA			2 (4%)
HEPATOCELLULAR CARCINOMA	1 (2%)	2 (4%)	1 (2%)
SARCOMA, NOS		1 (2%)	
#FORESTOMACH	(48)	(47)	(49)
PAPILLOMA, NOS		1 (2%)	2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(46)
ADENOMA, NOS	4 (9%)	7 (16%)	8 (17%)
#ADRENAL	(48)	(48)	(49)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	2 (4%)
#THYROID	(43)	(45)	(46)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(48)	(49)	(49)
SARCOMA, NOS		1 (2%)	
ENDOMETRIAL STROMAL POLYP	4 (8%)	2 (4%)	
#OVARY	(45)	(45)	(49)
PAPILLARY ADENOMA	1 (2%)		
TERATOMA, BENIGN	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(49)
ADENOMA, NOS	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	10	9	8
MORIBUND SACRIFICE	3	8	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	37	33	39
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	28	32
TOTAL PRIMARY TUMORS	41	34	43
TOTAL ANIMALS WITH BENIGN TUMORS	14	12	15
TOTAL BENIGN TUMORS	15	14	20
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	19	23
TOTAL MALIGNANT TUMORS	23	20	23
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3		
TOTAL UNCERTAIN TUMORS	3		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	106	103	106	106	106	106	106	106	106	106	106	106	106	106	095	105	106	106	106	106	085	106	106	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+	+ X
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
THYMUS	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER ADENOMATOUS POLYP, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	-	-	+	-	-	+	+	-	-	-	-	-	-	-	+	-	-	-	+	+	+	+	-	
PANCREATIC ISLETS ISLET-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N
TESTIS INTERSTITIAL-CELL TUMOR	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N X	N X	N X	N	N	N	N	N	N	N	N	N	N	N

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	02 6	02 7	02 8	02 9	03 0	03 1	03 2	03 3	03 4	03 5	03 6	03 7	03 8	03 9	04 0	04 1	04 2	04 3	04 4	04 5	04 6	04 7	04 8	04 9	05 0	TOTAL
WEEKS ON STUDY	1 0 6	1 0 6	1 0 6	0 9 6	1 0 6	0 8 9	1 0 6	0 0 1	1 0 6	1 0 6	0 8 4	1 0 6	1 0 6	1 0 6	1 0 3	1 0 6	1 0 6	1 0 6	1 0 6	0 9 2	1 0 6	1 0 6	1 0 1	1 0 6	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+ X	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	50 3 2
TRACHEA	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN MALIGNANT LYMPHOMA, NOS	+	+ X	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
LYMPH NODES	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	43
THYMUS	+	+	+	+	+	-	+	+	-	+	-	-	+	+	-	+	+	-	-	+	+	+	-	+	-	36
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+ X	+	+ X	+	+	+	+	+ X	+	+	+ X	+	+ X	50 7 3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER ADENOMATOUS POLYP, NOS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	49 1
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	-	+ X	+	+	+	+	+	-	+	+	-	-	+	-	+	44 1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+ X	+	+	+	-	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	49 2
PARATHYROID	-	-	+	-	+	-	+	+	+	+	-	+	-	-	+	+	-	+	-	-	-	+	+	+	-	22
PANCREATIC ISLETS ISLET-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS INTERSTITIAL-CELL TUMOR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS	N	N	N	N X	N	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N X	N	50* 1 5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	106	004	106	003	002	085	106	106	106	106	106	021	106	106	106	106	106	106	005	106	106	097	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																		X					X		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																		X					X		
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									X
LYMPH NODES	-	-	-	+	-	-	-	+	+	+	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
THYMUS	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA										X	X														
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+	+	+	+
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS								X																	
SMALL INTESTINE	+	+	-	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																									
THYROID	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	-	-	+	+	-	+	-	+	+	+	+	+	-	-	-	-	-	-	+	+	-	+	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																									
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS																								X	
LEUKEMIA,NOS																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	106	106	103	106	094	106	039	106	106	106	106	106	106	098	106	106	106	106	106	107	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+ X	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																							X			3
ALVEOLAR/BRONCHIOLAR CARCINOMA	X																									1
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										1
LYMPH NODES	-	-	+	+	-	-	-	-	+	+	-	+	+	-	A	+	-	+	+	+	+	+	-	+	+	29
MALIGNANT LYMPHOMA, NOS																								X		1
THYMUS	+	-	+	+	+	+	+	+	+	-	+	-	+	+	A	+	-	-	+	+	+	+	-	+	+	38
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA						X										X				X						5
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
PAPILLOMA, NOS																										1
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	+	+	+	-	+	+	+	+	43
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	+	-	A	+	+	-	+	+	+	+	+	+	+	43
ADENOMA, NOS								X																		1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA																			X						X	2
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	+	+	-	+	+	-	+	42
FOLLICULAR-CELL ADENOMA								X																		1
PARATHYROID	+	-	-	-	+	-	-	-	+	-	+	-	+	-	A	-	+	-	+	+	-	-	+	-	+	20
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR																							X			1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	-	+	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS		X									X															2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIGNANT LYMPHOMA, NOS							X							X					X							4
LEUKEMIA,NOS				X																						1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	041	106	002	106	102	106	103	064	053	075	106	106	006	106	106	103	106	106	106	104	106	106	088	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																X									
LEIOMYOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA		X			X	X																			
TRACHEA	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA											X														
LYMPH NODES	-	-	-	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
MALIGNANT LYMPHOMA, NOS															X										
THYMUS	-	+	+	-	-	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																		X			X			X	X
HEPATOCELLULAR CARCINOMA															X				X			X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	N	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS																								X	
SMALL INTESTINE	+	+	-	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	-	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	-	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	+	-	+	-	-	-	-	-	-	+	+	+	-	-	-	+	+	-	+	+	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS											X														
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LEIOMYOSARCOMA, METASTATIC																									
HEMANGIOSARCOMA																									
MALIGNANT LYMPHOMA, NOS				X	X							X		X						X	X		X		

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	103	106	106	098	106	106	106	106	106	106	106	106	106	106	103	106	106	106	070	106	100	106	051	106	098	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA																										1
LEIOMYOSARCOMA	X			X																						2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA											X													X		5
TRACHEA	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	44
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	41
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	+	-	-	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	-	35
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA								X																		3
HEPATOCELLULAR CARCINOMA																		X								4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PAPILLOMA, NOS																								X		2
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	43
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
ADENOMA, NOS											X															1
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	46
PARATHYROID	-	+	-	-	+	-	-	+	-	-	-	-	+	-	+	+	-	-	-	-	+	-	-	-	+	20
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS								X																		2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
LEIOMYOSARCOMA, METASTATIC	X			X																						2
HEMANGIOSARCOMA																									X	1
MALIGNANT LYMPHOMA, NOS					X					X		X			X											11

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	088	106	106	106	033	106	106	106	106	106	106	089	106	106	097	106	097	106	106	106	087	106	106	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE NEUROFIBROSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
TRACHEA	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPLEEN HEMANGIOSARCOMA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LYMPH NODES LEUKEMIA,NOS	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	X	+	+	
THYMUS MALIGNANT LYMPHOMA, NOS	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+ X	
CIRCULATORY SYSTEM																									
HEART	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LIVER HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																									
KIDNEY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	-	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	
ADRENAL	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
THYROID FOLLICULAR-CELL ADENOMA	+	-	+	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	
PARATHYROID	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	+	-	+	+	+	~	-	-	-	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
UTERUS ENDOMETRIAL STROMAL POLYP HEMANGIOMA	+	-	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	
OVARY PAPILLARY ADENOMA TERATOMA, BENIGN	+	-	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N X	N	N	N	N X	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N X	N	N	N	N X	N X	N X	N	N	N	N	N X	N	N X	N	N	N X	N	N	N X	N X	N
HEMATOPOIETIC SYSTEM NEOPLASM, NOS		X																							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	090	106	089	106	106	104	106	106	103	106	106	087	106	106	106	105	106	106	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE NEUROFIBROSARCOMA	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+ X	+	50M 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	+	46
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	-	+	+	+	-	+	+	47 1
LYMPH NODES LEUKEMIA,NOS	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	-	+	41 1
THYMUS MALIGNANT LYMPHOMA, NOS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	-	+	+	-		40 1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	47
LIVER HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+ X	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	N	+	+	N	+	+	+	N	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	-	+	+	-	+	+	+	-	+	+	42
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	+ X	+	+	+	+	+	-	+	-	+	+ X	+ X	+	+	+	+	-	+	+	-	+	+	+	44 4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	-	+	+	-	+	+		43 1
PARATHYROID	-	-	-	-	-	+	-	-	+	-	-	-	-	+	-	+	+	-	-	+	+	-	+	+		18
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	N	+	+	+	+	+	+	+ X	+	+	+	+ X	+	N	+	+	+	N	+	+	50M 2
UTERUS ENDOMETRIAL STROMAL POLYP HEMANGIOMA	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	-	+ X	+	+ X	+	+	+	48 4 1
OVARY PAPILLARY ADENOMA TERATOMA, BENIGN	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	45 1 1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M 2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N X	N	N	N	N	N	N	N X	N X	N	N	N X	N	N X	N	N	N	N	N	N	N X	N	N	50M 15
HEMATOPOIETIC SYSTEM NEOPLASM, NOS							X												X							3

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	106	100	106	106	101	106	106	106	081	106	095	106	106	091	105	106	106	106	106	106	106	106	087	101
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE OSTEOSARCOMA	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN MALIGNANT LYMPHOMA, NOS	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	-	-	-	+	+	+	-	-	+	-	-	+	-	-	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR CARCINOMA SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+ X	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH PAPILLOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+ X	+ X	+ X	+	+	+	+	+	+	+ X	+	+	+ X	+	+	-	+	-	+	+	+	+	+	+
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	-	+	+ X	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	+	-	+	-	-	-	-	-	-	+	+	+	-	-	-	-	-	+	+	+	-	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N
UTERUS SARCOMA, NOS ENDOMETRIAL STROMAL POLYP LYMPHANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+	+ X	+
OVARY	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BODY CAVITIES																									
MEDIASTINUM MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N	N	N X	N X	N X	N	N	N X	N	N X	N	N	N X	N	N	N	N	N X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	037	002	061	082	016	016	016	016	016	016	016	016	091	016	067	016	006	016	006	016	016	077	016	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE OSTEOSARCOMA	+	+	+	+	+ X	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50M 1	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	A	+	+	48
TRACHEA	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+	+	44
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	A	+	+	48
SPLEEN MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49 1
LYMPH NODES	–	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	–	+	+	A	+	+	41
THYMUS	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+	+	36
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	A	+	+	48
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+	+	47
LIVER HEPATOCELLULAR CARCINOMA SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	A	+	+	49 2 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	N	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49
STOMACH PAPILLOMA, NOS	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	A	+	+	47 1
SMALL INTESTINE	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	45
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	–	+	+	+	+ X	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+ X	+	43 7
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	–	+	+	+	+	A	+	+	48 1
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+	+	45 1
PARATHYROID	–	+	–	–	+	–	–	–	–	+	–	+	–	–	–	+	–	–	+	–	+	–	A	–	+	17
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS	+	N	N	+	N	+	+	+	+ X	+	+	+	+	+	+	+	+	N	+	N	+	+	N	+	+	50M 1
UTERUS SARCOMA, NOS ENDOMETRIAL STROMAL POLYP LYMPHANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+ X	+	49 1 2 1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	45
NERVOUS SYSTEM																										
BRAIN	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	A	+	+	46
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M 1
BODY CAVITIES																										
MEDIASTINUM MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M 1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N X	N	N	N X	N X	N	N X	N	N	N	N	N X	N	N	N	N	N	N	50M 12

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF DIALLYL PHTHALATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	082	106	106	106	035	011	106	106	106	106	106	106	106	094	102	106	104	106	106	106	106	106	064	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
															X										
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
								X										X					X		
TRACHEA	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	M	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
SPLEEN HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	M	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	M	+
THYMUS	+	-	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	-	+	+	-	+	+	M	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	M	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	M	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	+	+	+	M	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
STOMACH PAPILLOMA, NOS	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	M	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	M	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	-	+	-	+	-	+	+ X	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ X	M	+ X
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	M	-
PARATHYROID	+	-	-	-	-	+	+	+	-	+	-	+	+	-	+	-	-	-	+	+	+	-	+	M	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	M	+
UTERUS HEMANGIOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	M	+
OVARY HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	M	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N X	N X	N	N X	N X	N	N	N X	N X	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	106	106	106	106	106	106	082	106	103	106	099	106	106	106	106	085	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE HEMANGIOSARCOMA	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49* 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48 3
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	42
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	48 2 3
LYMPH NODES	+	-	+	+	+	+	+	+	+	-	+	-	-	-	+	+	-	+	+	+	+	+	+	+	+	40
THYMUS	+	-	+	+	+	+	-	+	-	-	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	49 2 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
PANCREAS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH PAPILLOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	46 8
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+ X	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	49 1 2
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	+	+	-	+	+	-	-	-	-	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	29
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
UTERUS HEMANGIOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1 1
OVARY HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N X	N	N	N X	N X	N	N	N X	N	N	N	N X	N	N	N	N	N X	N X	N	N	49* 15

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
ACANTHOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(46)	(47)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#LUNG	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
HEMORRHAGE	9 (18%)	7 (14%)	8 (16%)
BRONCHOPNEUMONIA, NOS	1 (2%)	1 (2%)	
INFLAMMATION, INTERSTITIAL	19 (38%)	19 (39%)	17 (34%)
PERIVASCULAR CUFFING		3 (6%)	
EPITHELIALIZATION			2 (4%)
METAPLASIA, SQUAMOUS		1 (2%)	
#LUNG/ALVEOLI	(50)	(49)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMATOPOIESIS		1 (2%)	
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#BONE MARROW	(49)	(47)	(47)
MYELOFIBROSIS	2 (4%)		1 (2%)
#SPLEEN	(49)	(48)	(50)
HYPERPLASIA, LYMPHOID	2 (4%)	2 (4%)	1 (2%)
HEMATOPOIESIS	1 (2%)	1 (2%)	1 (2%)
#LYMPH NODE	(43)	(29)	(41)
HEMOSIDEROSIS		1 (3%)	
PLASMACYTOSIS			1 (2%)
HYPERPLASIA, LYMPHOID		1 (3%)	
#MANDIBULAR L. NODE	(43)	(29)	(41)
HEMORRHAGE	1 (2%)		
#MEDIASTINAL L.NODE	(43)	(29)	(41)
HEMORRHAGE	1 (2%)		1 (2%)
#HEPATIC LYMPH NODE	(43)	(29)	(41)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(43)	(29)	(41)
HEMORRHAGE	10 (23%)	6 (21%)	4 (10%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
LYMPHOCYTOSIS		1 (3%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (3%)	
#INGUINAL LYMPH NODE	(43)	(29)	(41)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (5%)		
#LIVER	(50)	(49)	(50)
HEMATOPOIESIS	1 (2%)		1 (2%)
#THYMUS	(36)	(38)	(35)
CYST, NOS	1 (3%)		1 (3%)
LYMPHOID DEPLETION			1 (3%)
CIRCULATORY SYSTEM			
*SKIN	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#HEART	(50)	(49)	(50)
PERIVASCULAR CUFFING			1 (2%)
#MYOCARDIUM	(50)	(49)	(50)
MINERALIZATION		1 (2%)	1 (2%)
*TESTICULAR ARTERY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
#PANCREAS	(49)	(48)	(49)
POLYANGIITIS		1 (2%)	
*MESENTERY	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(47)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	20 (41%)	16 (34%)	9 (19%)
#LIVER	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	6 (12%)	6 (12%)
INFLAMMATION, MULTIFOCAL	3 (6%)	2 (4%)	1 (2%)
DEGENERATION, NOS	1 (2%)		
NECROSIS, NOS			1 (2%)
NECROSIS, COAGULATIVE	1 (2%)	2 (4%)	1 (2%)
INFARCT, NOS	4 (8%)		
METAMORPHOSIS FATTY	2 (4%)		
HEMOSIDEROSIS			1 (2%)
BASOPHILIC CYTO CHANGE		2 (4%)	1 (2%)
GROUND-GLASS CYTO CHANGE	8 (16%)	4 (8%)	9 (18%)
EOSINOPHILIC CYTO CHANGE	1 (2%)		
#PANCREAS	(49)	(48)	(49)
MINERALIZATION			1 (2%)
DILATATION/DUCTS		2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
#PANCREATIC ACINUS	(49)	(48)	(49)
ATROPHY, NOS		1 (2%)	1 (2%)
#STOMACH	(49)	(47)	(49)
MINERALIZATION	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
EROSION		1 (2%)	
INFECTION, PROTOZOAN			1 (2%)
#FORESTOMACH	(49)	(47)	(49)
CYST, NOS	1 (2%)		
ULCER, NOS		2 (4%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC		4 (9%)	8 (16%)
EROSION			1 (2%)
HYPERPLASIA, EPITHELIAL		7 (15%)	9 (18%)
#COLON	(48)	(47)	(47)
HEMORRHAGE	1 (2%)		
#CECUM	(48)	(47)	(47)
INFLAMMATION, CHRONIC		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
CALCULUS, NOS	2 (4%)	1 (2%)	
CYST, NOS			2 (4%)
PYELONEPHRITIS, NOS			3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR	36 (72%)	25 (51%)	26 (52%)
INFLAMMATION, INTERSTITIAL		3 (6%)	
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS	1 (2%)		
FIBROSIS, DIFFUSE		3 (6%)	1 (2%)
NEPHROPATHY		1 (2%)	
METAPLASIA, OSSEOUS	1 (2%)		2 (4%)
#URINARY BLADDER	(49)	(47)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	14 (29%)	10 (21%)	12 (24%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(42)
CYST, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(50)	(48)	(47)
CYST, NOS	1 (2%)		
#ADRENAL CORTEX	(50)	(48)	(47)
FOCAL CELLULAR CHANGE	1 (2%)	3 (6%)	4 (9%)
#ADRENAL MEDULLA	(50)	(48)	(47)
FOCAL CELLULAR CHANGE	1 (2%)		
#THYROID	(49)	(42)	(46)
THYROGLOSSAL DUCT CYST			1 (2%)
MINERALIZATION			1 (2%)
CYSTIC FOLLICLES	1 (2%)		
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)	
ABSCESS, NOS	2 (4%)		
INFLAMMATION, CHRONIC	7 (14%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		
#PROSTATE	(50)	(47)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	9 (18%)	9 (19%)	8 (16%)
INFLAMMATION, SUPPURATIVE		1 (2%)	2 (4%)
HYPERPLASIA, NOS		1 (2%)	
#TESTIS	(50)	(49)	(50)
MINERALIZATION	16 (32%)	14 (29%)	6 (12%)
GRANULOMA, NOS	2 (4%)		
DEGENERATION, NOS		3 (6%)	1 (2%)
CYTOMEGALY		1 (2%)	1 (2%)
HYPOSPERMATOGENESIS	3 (6%)		2 (4%)
*EPIDIDYMIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
GRANULOMA, NOS		2 (4%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
CALCULUS, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
PERIVASCULAR CUFFING	1 (2%)		
#BRAIN/THALAMUS	(50)	(50)	(50)
CALCULUS, NOS	15 (30%)	15 (30%)	18 (36%)
MINERALIZATION	1 (2%)	2 (4%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
NECROSIS, NOS	4 (8%)	3 (6%)	4 (8%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	3 (6%)	1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	8 (16%)	6 (12%)
INFLAMMATION, CHRONIC		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
AUTO/NECROPSY/HISTO PERF		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED DIALLYL PHTHALATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(48)
HEMORRHAGE	6 (12%)	11 (23%)	7 (15%)
INFLAMMATION, INTERSTITIAL	15 (30%)	13 (27%)	5 (10%)
PNEUMONIA, ASPIRATION	1 (2%)		
PERIVASCULAR CUFFING	6 (12%)	3 (6%)	4 (8%)
PARAMYLOID		1 (2%)	
EPITHELIALIZATION		1 (2%)	
#LUNG/ALVEOLI	(50)	(48)	(48)
HISTIOCYTOSIS	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BRAIN	(50)	(46)	(49)
HEMATOPOIESIS	1 (2%)		
*MULTIPLE ORGANS	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID	2 (4%)		1 (2%)
#BONE MARROW	(46)	(48)	(49)
MYELOFIBROSIS	44 (96%)	39 (81%)	46 (94%)
#SPLEEN	(47)	(49)	(48)
ANGIECTASIS	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	5 (10%)
HEMATOPOIESIS	4 (9%)	1 (2%)	1 (2%)
#LYMPH NODE	(41)	(41)	(40)
HEMORRHAGE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PLASMACYTOSIS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#MEDIASTINAL L.NODE	(41)	(41)	(40)
PARAMYLOID		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (5%)		
#MESENTERIC L. NODE	(41)	(41)	(40)
HEMORRHAGE	3 (7%)	1 (2%)	1 (3%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(41)	(41)	(40)
HYPERPLASIA, LYMPHOID			1 (3%)
*STERNUM	(50)	(50)	(49)
MYELOFIBROSIS		1 (2%)	
#LUNG	(50)	(48)	(48)
HYPERPLASIA, LYMPHOID	2 (4%)		
#LIVER	(50)	(49)	(49)
HEMATOPOIESIS	1 (2%)	1 (2%)	
#ILEUM	(42)	(45)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	
#ADRENAL	(48)	(48)	(49)
HEMATOPOIESIS			1 (2%)
#THYMUS	(40)	(36)	(37)
HYPERPLASIA, LYMPHOID	3 (8%)		
CIRCULATORY SYSTEM			
#HEART	(49)	(48)	(48)
MINERALIZATION			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(47)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	9 (19%)	6 (13%)	8 (17%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE			1 (2%)
#LIVER	(50)	(49)	(49)
DILATATION/DUCTS			1 (2%)
TORSION			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (14%)	7 (14%)	18 (37%)
INFLAMMATION, MULTIFOCAL	11 (22%)	12 (24%)	8 (16%)
NECROSIS, COAGULATIVE	1 (2%)	2 (4%)	2 (4%)
INFARCT, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
BASOPHILIC CYTO CHANGE		1 (2%)	2 (4%)
GROUND-GLASS CYTO CHANGE	2 (4%)	4 (8%)	4 (8%)
#PANCREAS	(47)	(48)	(48)
DILATATION/DUCTS	2 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	3 (6%)
#PANCREATIC ACINUS	(47)	(48)	(48)
ATROPHY, NOS	3 (6%)		
#STOMACH	(48)	(47)	(49)
MINERALIZATION		2 (4%)	
INFECTION, PROTOZOAN			1 (2%)
#FORESTOMACH	(48)	(47)	(49)
ULCER, NOS	1 (2%)	1 (2%)	
INFLAMMATION, SUPPURATIVE			2 (4%)
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	9 (18%)
HYPERPLASIA, EPITHELIAL	4 (8%)	1 (2%)	14 (29%)
#CECUM	(46)	(47)	(49)
PARASITISM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(48)	(49)	(49)
HYDRONEPHROSIS		1 (2%)	
HEMORRHAGE		1 (2%)	
GLOMERULONEPHRITIS, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	23 (48%)	25 (51%)	27 (55%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
FIBROSIS, DIFFUSE	1 (2%)	1 (2%)	1 (2%)
DEGENERATION, HYALINE		1 (2%)	
DEGENERATION, HYDROPIC	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
METAPLASIA, OSSEOUS			1 (2%)
#KIDNEY/TUBULE	(48)	(49)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#URINARY BLADDER	(48)	(50)	(48)
DILATATION, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	18 (38%)	26 (52%)	22 (46%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(46)
CYST, NOS			1 (2%)
HEMORRHAGE			1 (2%)
FOCAL CELLULAR CHANGE	5 (11%)	1 (2%)	2 (4%)
ANGIECTASIS	1 (2%)		
#ADRENAL	(48)	(48)	(49)
CYST, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
LIPOIDOSIS		1 (2%)	
#ADRENAL CORTEX	(48)	(48)	(49)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	4 (8%)
#ADRENAL MEDULLA	(48)	(48)	(49)
FOCAL CELLULAR CHANGE	2 (4%)	1 (2%)	
#THYROID	(43)	(45)	(46)
FOLLICULAR CYST, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#PARATHYROID	(18)	(17)	(29)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (6%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
DILATATION/DUCTS		1 (2%)	3 (6%)
*VAGINA	(50)	(50)	(49)
INFLAMMATION, CHRONIC	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL	1 (2%)		
#UTERUS	(48)	(49)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
METAPLASIA, SQUAMOUS	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(49)	(49)
CYST, NOS	2 (4%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	40 (83%)	42 (86%)	45 (92%)
#OVARY	(45)	(45)	(49)
MINERALIZATION		1 (2%)	
FOLLICULAR CYST, NOS	4 (9%)	6 (13%)	8 (16%)
PAROVARIAN CYST	8 (18%)	6 (13%)	3 (6%)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE		2 (4%)	
INFLAMMATION, CHRONIC			1 (2%)
ANGIECTASIS	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(46)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
#BRAIN	(50)	(46)	(49)
HEMORRHAGE		1 (2%)	
PERIVASCULAR CUFFING	1 (2%)		
MALACIA	1 (2%)		
#BRAIN/THALAMUS	(50)	(46)	(49)
CALCULUS, NOS	16 (32%)	20 (43%)	31 (63%)
MINERALIZATION	1 (2%)	6 (13%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(49)
NECROSIS, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*FEMUR	(50)	(50)	(49)
FIBROUS OSTEODYSTROPHY		1 (2%)	
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(49)
NECROSIS, FAT			1 (2%)
*PERITONEUM	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
*MESENTERY	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	13 (26%)	6 (12%)	8 (16%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	
ANIMAL MISSING/NO NECROPSY			1
AUTO/NECROPSY/HISTO PERF		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX C

ANALYSIS OF DIALLYL PHTHALATE
MIDWEST RESEARCH INSTITUTE

APPENDIX C

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	68.28	5.73
Determined	68.38	5.69
	68.22	5.80

B. WATER ANALYSIS

(Karl Fisher) 0.144 ± 0.004 (δ) %

C. BOILING POINT

Determined

b.p. 160°-161°C/5 mm Hg (macro distillation)

Literature Values

b.p. 165°-167°C/5 mm Hg (Beilstein)

D. INDEX OF REFRACTION

Determined

n_D^{20} 1.5184

Literature Values

n_D^{20} 1.5203 (Beilstein)

E. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel F: 254

Amount Spotted: 100 and 300 μg

Ref. Standard: Dimethyl terephthalate

Detection Systems: Ultraviolet (254 mm) and iodine vapor

System 1: Methanol (100%)
R_f: 0.85
R_{st}: 1.04

System 2: Benzene (100%)
R_f: 0.25
R_{st}: 1.18

F. GAS-LIQUID CHROMATOGRAPHY

Instrument: Tracor MT 220
Column: 3% OV-17, 1.8 m x 4 mm I.D.
Detector: Flame ionization
Oven Temperature Program: 100°C, 5 min; 100°-235°C at 10°C/min
Results: Major peak and eight impurities

Peak	Retention Time (min)	Retention Time (Relative to Diallyl Phthalate)	Area (Relative to Diallyl Phthalate Peak)
1	8.8	0.56	0.106
2	10.6	0.67	0.046
3	11.2	0.71	0.064
4	13.0	0.82	trace
5	13.2	0.84	trace
6	14.8	0.94	0.045
7	15.8	1.00	1.00
8	17.4	1.10	0.074
9	18.0	1.14	0.731

G. SPECTRAL DATA

1. Infrared:
   Instrument: Beckman IR-12
   Cell: Neat liquid on sodium chloride plates
   Results: See Figure 4

   Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible:
   Instrument: Cary 118

λ Max (nm)	ε x 10^{-3}	Literature Values (Sadtler Standard Spectra) λ Max (nm)	ε x 10^{-3}
225	8.3 ± 0.5 (δ)	225	8.5
275	1.2 ± 0.1 (δ)	275	1.3

   No maximum observed between 350 nm and 800 nm at 0.15 mg/ml
   Solvent: 95% Ethanol

3. Nuclear Magnetic Resonance:
   Instrument: Varian HA-100
   Solvent: Neat liquid with added internal tetramethylsilane
   Assignments: See Figure 5

   Consistent with literature spectrum (Sadtler Standard Spectra)

   a = δ 4.72 ppm (J_{ab} = 1.5 H_z, J_{ad} = 5 H_z);
   b = δ 5.12 ppm (J_{bc} □ 2 H_z, J_{bd} = 10 H_z);
   c □ δ 5.26 ppm (J_{cd} □ 18 H_z);
   d = δ 5.73-6.15 ppm;
   e = δ 7.35-7.51 ppm;
   f = δ 7.57-7.73 ppm.

   Integration Ratios:

   a = 3.82
   b = 1.84
   c = 2.18
   d = 2.08
   e □ 2.01
   f = 2.08

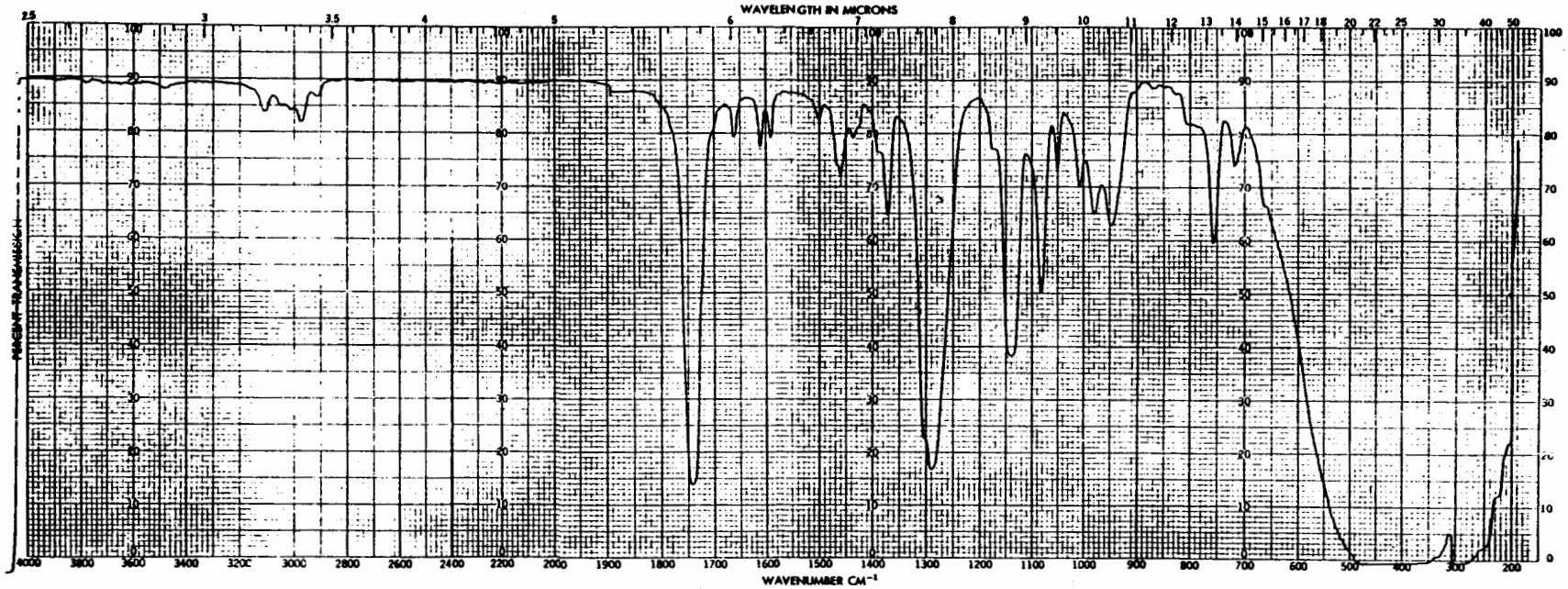

Figure 4. Infrared Absorption Spectrum of Diallyl Phthalate (Lot No. 25-121)

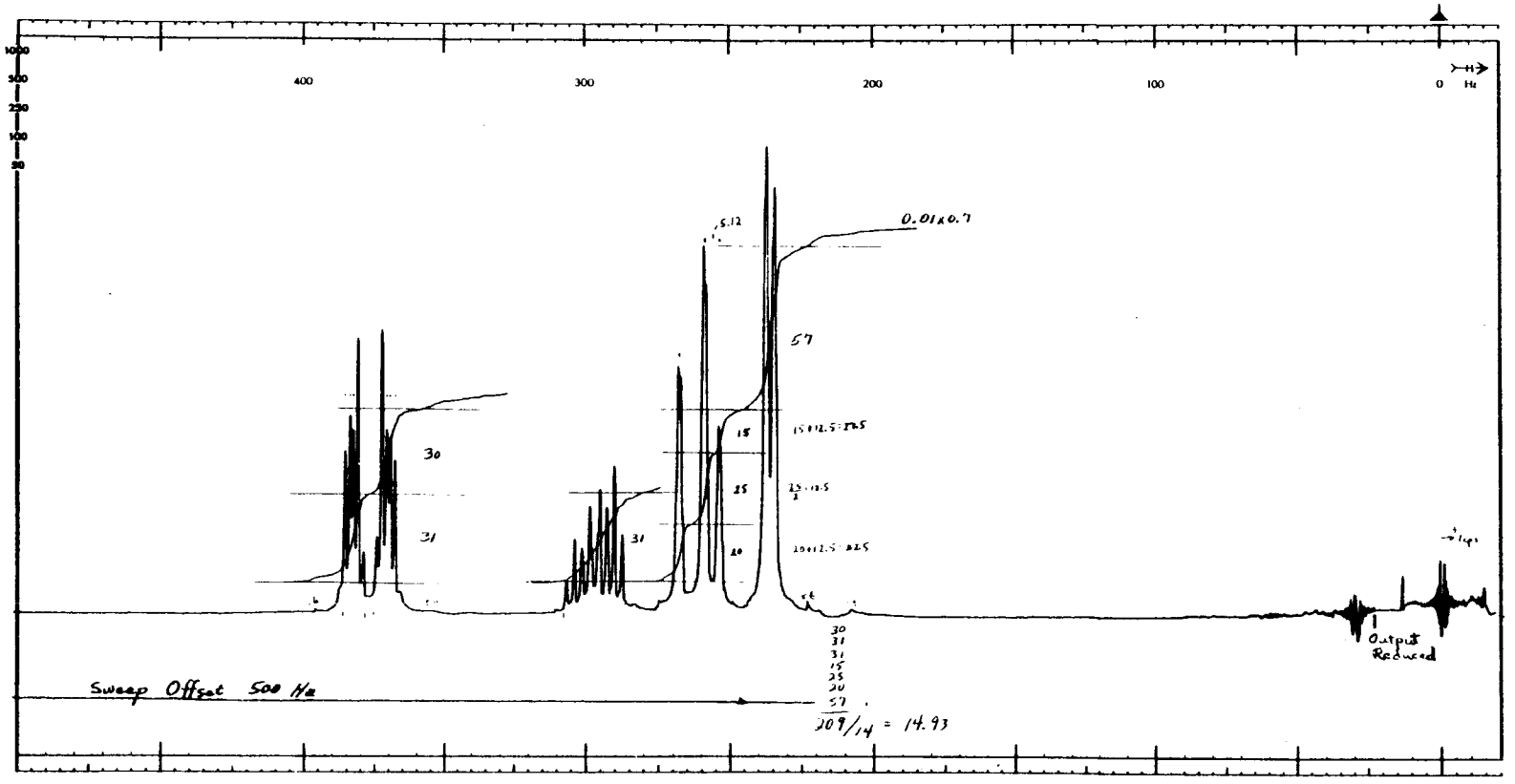

Figure 5. Nuclear Magnetic Resonance Spectrum of Diallyl Phthalate (Lot No. 25-121)

APPENDIX D

ANALYSES OF DIALLYL PHTHALATE/CORN OIL MIXTURES FOR STABILITY OF DIALLYL PHTHALATE

APPENDIX D

A. SAMPLE PREPARATION AND STORAGE

One milliliter of corn oil was sealed (septum and aluminum crimp-seal, Wheaton Scientific) in an 8-ml septum vial. The vial was weighed, and approximately 80 μl of diallyl phthalate was injected by micro syringe. The vial was reweighed to determine the actual amount of diallyl phthalate added. Twenty-four samples were prepared in this manner and thoroughly shaken to mix the vial contents. Twelve of the samples were stored at room temperature (25°C) with no attempt to protect them from light. The other 12 samples were stored in a refrigerator at 5°C. Two samples from each storage temperature were analyzed at various intervals over a 15-day period.

B. EXTRACTION AND ANALYSIS

The diallyl phthalate was extracted from the corn oil by injecting 4 ml of methanol into the septum vials, followed by 15 seconds of vigorous manual shaking of the vials. After the methanol and corn oil layers had separated (approximately 15 minutes), 5 μl aliquots of the methanol solution were injected directly into a gas chromatograph for analysis.
Instrument: Bendix 2500 or Tracor MT-220

1. System 1
   Column: 3% OV-1 on Supelcoport DMCS, 80/100 mesh, 4 mm x 1.8 m, glass
   Oven temperature: 170°C, isothermal
   Inlet temperature: 205°C
   Detector temperature: 255°C
   Detection: Flame ionization
2. System 2
   Column: 3% DEGS on Gas Chrom P, 80/100 mesh, 4 mm x 1.8 m, glass
   Oven temerature: 195°C, isothermal
   Inlet temperature: 205°C
   Detector temperature: 255°C
   Detection: Flame ionization

   Systems 1 and 2 were used interchangeably, depending on instrument availability.

C. RESULTS

Storage Time Prior to Analysis (days)	Column	Average Percent in Chem./Vehicle Mixture *(a)*	
		at 25°C	at 5°C
1	OV-1	—	9.27 ± 0.28
2	OV-1	9.11 ± 0.31	9.22 ± 0.28
5	OV-1	8.57 ± 0.44	8.85 ± 0.43
8	OV-1	8.67 ± 0.40	8.83 ± 0.46
10	DEGS	9.37 ± 0.38	9.02 ± 0.40
15	DEGS	9.07 ± 0.29	9.16 ± 0.40

(a) Corrected for a spike recovery yield: 84.2% ± 2.5% of theoretical. Average theoretical (actual) compound added to corn oil: 9.01%.

D. CONCLUSION

All of the corrected analytical values are within ± 0.45% units of the mean value, 9.02%. This represents a mean percentage recovery of 84.2 ± 4.2, which compares very well with the spiked recovery yield of 84.2% ± 2.5%. Therefore, diallyl phthalate mixed with corn oil at the 9.0% (w/v) level is stable for 15 days at temperatures of 25°C or below.

E. STORAGE CONDITIONS FOR MIXTURES IN CORN OIL

Diallyl phthalate mixed with corn oil at the 9.0% (w/v) level may be stored in closed containers in the presence of light for a period of 2 weeks at room temperature (25° C) or for at least 8 weeks at 5° C. This latter storage time is extrapolated from the above stability study at 25° C. Further conclusions regarding the stability of diallyl phthalate mixed with corn oil cannot be drawn from this study.

APPENDIX E

ANALYSES OF DIALLYL PHTHALATE/CORN OIL MIXTURES FOR CONCENTRATIONS OF DIALLYL PHTHALATE

APPENDIX E

A. CARBON DISULFIDE EXTRACTION METHOD

An aliquot of the corn oil dosage mixture was diluted with carbon disulfide. The solution was mixed well. Analysis was performed by gas-liquid chromatography. The concentration of the test compound was determined by reference to a calibration curve prepared by analysis of a standard solution of diallyl phthalate.

A stock standard solution of diallyl phthalate was prepared by dissolving 300 mg of the compound to a final volume of 50 ml with carbon disulfide.

Three milliliters of carbon disulfide was added to samples of diallyl phthalate/corn oil mixture containing approximately 15 mg diallyl phthalate and mixed by shaking on an automatic shaker box for 10 minutes.

Approximately 2 ml of each sample was transferred with a disposable syringe into septa vials suitable for the automatic sampler.

Instrument Parameters:

Instruments: Hewlett-Packard 5840A with a 7672 Automatic Liquid Sampler
Detector: Flame ionization
Column temperature: 210°C
Injector temperature: 225°C
FID temperature: 250°C
Column: 1.8 m x 2 mm I.D. glass-packed with 3% OV-17 on 80/100 mesh supelcoport
Chart: 1.00 cm/minute
Flow: 20 cc/min nitrogen
Method of calibration: External standard

B. METHANOL EXTRACTION METHOD

An aliquot of the corn oil dosage mixture was extracted with methanol, containing triphenylmethane as an internal standard. The concentration of the test compound was determined by reference to a calibration curve prepared by analysis of a set of diallyl phthalate working standards.

Twenty milliliters of the internal standard solution was added to 2.0 ml of diallyl phthalate/corn oil solutions. Samples were mixed on a Vortex mixer for 30 seconds, sonicated for 30 seconds, and centrifuged for 3 minutes at 1,200 rpm.

Approximately 1 ml of the solvent layer was transferred via disposable pipettes into septa vials for the automatic sampler.

Instrument Parameters:

Column temperature: 200°C
Injection temperature: 250°C
Detector temperature: 270°C
Flow rate: 30 ml/min.
Chart speed: 0.5 cm/min.
Inj. volume: 3 μl

C. RESULTS

See Table E1.

TABLE E1. ANALYSES OF CORN OIL MIXTURES

Date Mixed	Week Used	Concentration of Diallyl Phthalate in Corn Oil for Target Concentration *(a)* of 15 mg/ml	30 mg/ml
CARBON DISULFIDE EXTRACTION			
11/22/78	11/23	14.9	
12/19/78	12/20		30.1
01/19/79	01/20	15.5	30.8
02/06/79	02/07	15.3	
02/12/79	02/13	13.5	28.5
03/06/79	03/07	14.4	
04/03/79	04/04		30.2 (30.3)b
05/01/79	05/02	17.2	
05/29/79	05/30		29.6
06/19/79	06/20	14.1 *(c)*	27.6 *(c)*
06/26/79	06/27	14.9	
07/24/79	07/26	14.8	28.8
07/25/79	07/26		29.8
08/21/79	08/22	14.3	
09/18/79	09/20		30.3 (26.9)b
Mean (mg/ml)		14.9	29.5
Standard deviation		1.00	1.02
Coefficient of variation (%)		6.7	3.5
Range		14.1-17.2	28.5-30.8
Number of samples		10	9
METHANOL EXTRACTION			
10/16/79	10/17	15.4	
11/13/79	11/14		31.9
11/22/79	11/23	14.3	
12/11/79	12/12	16.0	
01/08/80	01/09		29.4
02/05/80	02/06	14.8 (15.2)b	29.6
03/04/80	03/05	14.6	29.6
04/01/80	04/02	16.0	
06/24/80	06/25		29.6
07/22/80	07/23	15.3	
Mean (mg/ml)		15.2	30.0
Standard deviation		0.7	1.05
Coefficient of variation (%)		4.4	3.5
Range (mg/ml)		14.3-16.0	29.4-31.9
Number of samples		7	5

(a) The data presented are the average of the results of duplicate analyses.
(b) The number in parentheses is the MRI chemical/vehicle referee result.
(c) Reanalysis results.

APPENDIX F

MEAN BODY WEIGHTS OF MICE ADMINISTERED DIALLYL PHTHALATE IN THE TWO-YEAR STUDY

TABLE F1. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF MICE ADMINISTERED DIALLYL PHTHALATE BY GAVAGE IN THE TWO-YEAR STUDY

	Mean Body Weight (Grams)			Body Weight Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
2	28	27	27		
3	28	27	26	–4	–7
25	36	36	36	0	0
45	38	38	38	0	0
65	39	39	39	0	0
85	37	39	38	+5	+3
105	38	37	36	–3	–5
Females					
2	21	21	21		
3	21	21	21	0	0
25	27	27	28	0	+4
45	29	30	30	+3	+3
65	32	32	32	0	0
85	34	33	33	–3	–3
105	33	33	33	0	0

(a) Weight of the dosed group relative to that of the controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

APPENDIX G

HISTORICAL INCIDENCE OF TUMORS IN B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE

TABLE G1. HISTORICAL INCIDENCE OF STOMACH OR FORESTOMACH PAPILLOMAS IN B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Males	Females
Frederick	0/50 (0%)	1/50 (2.0%)
Gulf South	1/175 (0.6%)	2/197 (1.0%)
Litton	1/117 (0.9%)	0/115 (0%)
Mason	0/50 (0%)	0/50 (0%)
Papanicolaou	0/48 (0%)	0/47 (0%)
Southern	1/198 (0.5%)	0/197 (0.5%)
Total *(b)*	3/638 (0.5%)	3/656 (0.5%)

(a) Data as of June 15, 1981 for studies of at least 104 weeks.
(b) Includes papillomas identified as NOS or squamous cell.

TABLE G2. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Lymphoma	Lymphoma or Leukemia
Frederick	0/50 (0%)	0/50 (0%)
Gulf South	17/191 (8.9%)	25/191 (13.1%)
Litton	18/120 (15.0%)	19/120 (15.8%)
Mason	6/50 (12.0%)	6/50 (12.0%)
Papanicolaou	11/50 (22.0%)	11/50 (22.0%)
Southern	19/200 (9.5%)	19/200 (9.5%)
Total	71/661 (10.7%)	80/661 (12.1%)
Overall Historical Range		
High	11/50 (Papanicolaou)	15/48 (Gulf South)
Low	0/50 (Frederick)	0/50 (Frederick)

(a) Data as of June 15, 1981 for studies of at least 104 weeks. Range is presented for groups of 35 or more animals.

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