NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 298

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

(CAS NO. 597-25-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

(CAS No. 597-25-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

January 1986

NTP TR 298

NIH Publication No. 86-2554

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

NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis 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 has the potential for 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.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes 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. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

CONTENTS

TABLES

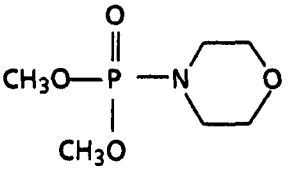
TABLES (Continued)

FIGURES

APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)



DIMETHYL MORPHOLINOPHOSPHORAMIDATE

CAS No. 597-25-1

Synonyms: Dimethyl morpholinophosphonate; Phosphonic acid, morpholino, dimethyl ester; DMMPA; Phosphonic acid, 4-morpholinyl-, dimethyl ester

$C_6H_{14}NO_4P$ Molecular weight: 195.16

ABSTRACT

Dimethyl morpholinophosphoramidate (DMMPA, greater than 99% pure) was developed for use as a simulant for the physical (but not biologic) properties of anticholinesterase agents in chemical defense training. Because of the potential for human exposure, the toxicity and carcinogenicity of DMMPA were investigated. Fourteen-day and 13-week studies were conducted to determine short-term toxicity, to identify target organs, and to establish doses for the 2-year toxicology and carcinogenesis studies.

In the 14-day studies, groups of five male and five female F344/N rats were administered DMMPA in corn oil by gavage daily at 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg body weight for 14 consecutive days. All the rats receiving DMMPA at 2,500 or 5,000 mg/kg, except one male receiving 5,000 mg/kg, died before the end of the studies. Rats receiving DMMPA at doses of 1,250 mg/kg or less survived. The final mean body weights of the surviving dosed rats were within ± 8% of those of the vehicle controls. Compound-related gross lesions were not found at necropsy. Groups of five $B6C3F_1$ mice of each sex were given DMMPA by the same route on the same schedule at 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg. All the mice given DMMPA at 2,000 or 4,000 mg/kg died before the end of the studies. Mice administered DMMPA at doses of 1,000 mg/kg or less survived. The final mean body weight of the male mice given DMMPA at 1,000 mg/kg was 14% greater than that of the vehicle controls, whereas that of the other dosed survivors was within 10% of that of the vehicle controls. Compound-related gross lesions were not found at necropsy.

In the 13-week studies, groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice were given DMMPA by gavage in corn oil at 0, 200, 400, 800, 1,200, or 1,600 mg/kg body weight, 5 days per week for 13 weeks. All rats given DMMPA at 400 mg/kg or less survived, and no more than 3/10 died in any of the higher dose groups. The final mean body weights of the dosed male rats were 6% to 11% greater than that of the vehicle controls; weights of the dosed female rats were similar to that of the vehicle controls (−6% to 1%). There was a dose-related increase in liver weight/body weight ratio.

All the mice given DMMPA at 1,600 mg/kg, except one female, died before the end of the 13-week studies; mice receiving DMMPA at 1,200 mg/kg or less survived. The final mean body weights of the dosed male mice were 3.4% to 6.9% greater than that of the vehicle controls. The final mean body weights of dosed female mice and vehicle controls were similar. Compound-related gross or histopathologic changes were not observed in rats or mice.

In the 2-year toxicology and carcinogenesis studies, groups of 50 male and 50 female F344/N rats were given DMMPA in corn oil by gavage at doses of 0, 150, 300, or 600 mg/kg body weight, 5 days per week for 103 weeks. Groups of 50 male $B6C3F_1$ mice were given DMMPA at 0, 150, or 300 mg/kg body weight, and groups of 50 female $B6C3F_1$ mice were given DMMPA at 0, 300, or 600 mg/kg body weight on the same schedule. Doses of 300 or 600 mg/kg were originally selected for male mice for the 2-year study; because 19/50 high dose male mice died by week 19, all male mice were killed and doses of 0, 150, and 300 mg/kg were selected for the restart of the 2-year study in male mice. The survival of high dose male (22/50) and female (24/50) rats was reduced ($P<0.025$) relative to that of the male (37/50) and female (36/50) vehicle controls. Mean body weights were less than 10% lower in the mid dose and high dose male rats and in the high dose female rats than in the vehicle controls. DMMPA administration did not significantly affect body weight gain or survival of male and female mice.

At the 600 mg/kg dose, increased ($P<0.05$) incidences of mononuclear cell leukemia occurred in both male rats (vehicle control, 14/50; 150 mg/kg, 21/50; 300 mg/kg, 19/50; 600 mg/kg, 25/50) and female rats (9/50; 13/50; 12/49; 18/50). DMMPA-related neoplastic or nonneoplastic lesions were not observed in the dosed mice.

DMMPA was not mutagenic in strains TA100, TA1535, TA1537, or TA98 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9. DMMPA was mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma assay in the absence of S9; it was not tested in the presence of S9. DMMPA induced chromosomal aberrations and sister-chromatid exchanges in Chinese hamster ovary cells in the absence of S9, but cytogenetic effects were not observed in the presence of Aroclor 1254-induced rat liver S9.

An audit of the experimental data for these 2-year carcinogenesis studies on DMMPA was conducted. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenicity** for male and female F344/N rats given dimethyl morpholinophosphoramidate, as indicated by increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenicity* for male and female $B6C3F_1$ mice given dimethyl morpholinophosphoramidate at doses of 150 (male), 300, or 600 (female) mg/kg for 2 years.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dimethyl Morpholinophosphoramidate is based on the 13-week studies that began in October 1978 and ended in January 1979 and on the 2-year studies that began in April 1980 (rats), May 1980 (female mice), and January 1981 (male mice) and ended in May 1982 (rats and female mice) and January 1983 (male mice) at Litton Bionetics, Inc.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

Po C. Chan, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
David M. DeMarini, Ph.D.
June Dunnick, Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
W.M. Kluwe, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on 2/10/83 For Rats and Female Mice)

Robert M. Sauer, V.M.D. (Chair)
(Clement Associates)
Ken Ayres, D.V.M., Ph.D.
(Burroughs Wellcome Co.)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Hendricus Solleveld, D.V.M., Ph.D. (NTP)
Marilyn J. Wolfe, D.V.M., Ph.D. (NTP)

(Evaluated Slides and Prepared Pathology Report on 7/29/83 For Male Mice)

Hendricus Solleveld, D.V.M., Ph.D. (Chair) (NTP)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Leroy Hall, D.V.M., Ph.D. (Observer) (NTP)
A.W. Macklin, D.V.M., Ph.D.
(Burroughs Wellcome Laboratories)
K. Yoshitomi, D.V.M., Ph.D. (Observer) (NTP)

Principal Contributors at Litton Bionetics Inc.
(Conducted Studies and Evaluated Tissues)

Carter Johnston, Ph.D.
Principal Investigator
Allan Manus, D.V.M.
Principal Investigator
Jerry M. Fitzgerald, Ph.D.
Chemist
Richard H. Cardy, D.V.M.
Pathologist for rats
James Moe, D.V.M.
Pathologist for mice

Principal Contributors at Experimental Pathology Laboratory
(Provided Pathology Quality Assurance)

Jerry Hardisty, D.V.M.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Project Manager
Abigail C. Jacobs, Ph.D.
Senior Scientist
John Warner, M.S.
Chemist/Statistician

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on DMMPA on November 2, 1984, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

Curtis Harper, Ph.D. (Principal Reviewer)
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

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

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D.*
Board on Toxicology and Environmental Health Hazards
National Academy of Sciences
Washington, D.C.

Seymour L. Friess, Ph.D.
Arlington, Virginia

Thomas C. Jones, D.V.M.
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V. M., Ph.D.
(Principal Reviewer)
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D.
Director, Environmental Health Sciences Program
Hunter School of Health Sciences
New York, New York

Tom Slaga, Ph.D.
Science Park, Research Division
University of Texas System Cancer Center
Smithville, Texas

Steven R. Tannenbaum, Ph.D.*
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D.
Professor and Associate Director
College of Engineering
Cornell University
Ithaca, New York

John R. Van Ryzin, Ph.D. (Principal Reviewer)
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

On November 2, 1984, the draft Technical Report on the toxicology and carcinogenesis studies of dimethyl morpholinophosphoramidate (DMMPA) received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The 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.

Dr. Kociba, a principal reviewer, agreed in principle with the conclusion; however, he did question the interpretation that F344/N rat leukemia in female rats supported some evidence of carcinogenicity. Based on the historical control incidence range (16% to 42%) that bracketed the rates for all dosed female groups, he favored a designation of equivocal evidence of carcinogenicity. Dr. P. Chan, NTP, explained that the conclusion of some evidence of carcinogenicity in rats was supported by a comparison with concurrent controls and by this being the first study completed by the NTP in which there were significant increases in the incidences of mononuclear cell leukemia in both male and female rats. On two other issues, Dr. Kociba said that cholinesterase monitoring might have helped to define the toxicity that necessitated a restarting of the studies in male mice and, given the projected use for DMMPA, dermal application may have been a more appropriate route of exposure.

As a second principal reviewer, Dr. Van Ryzin agreed with the conclusions. He said that the survival data suggest that the estimated maximal tolerated dose was exceeded for high dose male and female rats and for female mice but that the life table test adequately adjusted for this and the results were not compromised. Dr. Van Ryzin thought that more supporting information was needed before the liver could be considered the site of DMMPA detoxification and that liver enlargement was related to microsomal enzyme induction; he also suggested that the speculation that genetic toxicity was the basis for carcinogenicity of DMMPA should be deleted. Mr. Beliczky considered that the increase in liver weight was an important observation and the speculation was reasonable.

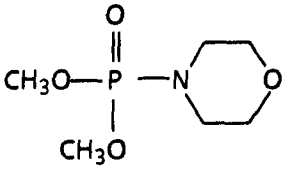
As a third principal reviewer, Dr. Harper stated he would have interpreted the rat leukemia data as clear evidence of carcinogenicity for both sexes and given more weight to concurrent control data. He also thought that there was equivocal evidence of carcinogenicity in male mice based on the positive trend for hepatocellular carcinomas. Dr. Chan explained that pairwise comparisons did not show statistically significant increases for hepatocellular carcinomas and combining those with the incidences of heptocellular adenomas eliminated the positive trend; he said that some evidence of carcinogenicity was chosen for the leukemias rather than clear evidence of carcinogenicity because the incidences were increased only at the high dose and this is a relatively common neoplasm in F344/N rats. Dr. Swenberg commented that the grading of the lesions into stages as reported tended to support a high-dose effect and the appropriateness of some evidence of carcinogenicity.

In further discussion concerning the mononuclear cell leukemias in rats, Dr. Friess suggested that since the leukemias are malignant in all stages, clear evidence of carcinogenicity was supported. Dr. G. Boorman, NTP, indicated that this lesion was common in the F344/N rat and was variable among different control groups. Dr. J. Haseman, NIEHS, added that there was lack of agreement between the results of the incidental tumor test and the life table test, even though the life table test was more appropriate for the lesion, since leukemias are lethal. Dr. E. McConnell and Dr. J. Huff, NTP, commented that the criteria for assigning the categories of evidence as currently used by the NTP should not be considered too narrowly and these should be used with sufficient latitude for interpretation of the wide variations of experimental outcomes.

Dr. Van Ryzin moved that the Technical Report on the toxicology and carcinogenesis studies of dimethyl morpholinophosphoramidate be accepted. Dr. Swenberg seconded the motion, and the report was approved by nine affirmative votes. There was one negative vote (Mr. Beliczky).

I. INTRODUCTION

I. INTRODUCTION



DIMETHYL MORPHOLINOPHOSPHORAMIDATE

CAS No. 597-25-1

Synonyms: Dimethyl morpholinophosphonate; Phosphonic acid, morpholino, dimethyl ester; DMMPA; Phosphonic acid, 4-morpholinyl-, dimethyl ester

$C_6H_{14}NO_4P$ Molecular weight: 195.16

The Canadian Defence Research Establishment, Suffield, Canada, developed dimethyl morpholinophosphoramidate (DMMPA), an organophosphate, for use as a simulant for the physical (but not the biologic) properties of nerve agents in chemical defense training. The U.S. Army and its allied forces have considered the use of DMMPA in their chemical defense training programs. The use of DMMPA for other purposes is not known. The compound is not produced commercially in the United States, and import figures are not available.

DMMPA is a clear, colorless liquid with an odor reminiscent of choline. Various properties of DMMPA are given in Table 1.

The LD_{50} values of DMMPA in albino mice (strain unspecified) were 0.4 g/kg body weight intravenously, 3.3 g/kg orally, 4.8 g/kg intramuscularly, and 5.0 g/kg intraperitoneally; in albino rats (strain unspecified), 6 g/kg orally, 5.2 g/kg intramuscularly, and 2.4 g/kg intraperitoneally; and in New Zealand rabbits, 0.35 g/kg intravenously (Coleman, 1977a). Death was due to respiratory failure in these species.

In rats, a single oral dose (3.5-5.8 g/kg) of DMMPA decreased blood pressure, heart rate, and respiratory rate. The rats that died after a single dose (higher than 5.4 g/kg) of DMMPA had congested lungs with hemorrhage in the alveolar space. The liver and kidneys also were congested. Nonfatal doses (less than 5.4 g/kg) of DMMPA caused no discernable morphologic and physiologic changes (Coleman, 1977a).

Daily dermal application of DMMPA to rats (20 µl) and to New Zealand rabbits (100 µl) for 4 weeks induced no histologic changes at the site of application or in other organs (McNally and Adie, 1977). New Zealand rabbits given 62 mg (30 mg/kg) or 123 mg (60 mg/kg) of DMMPA by skin application, 5 days a week for 20 weeks, showed no signs of skin lesions (Coleman, 1977b). No morphologic or physiologic effects were demonstrated in male or female rats (strain unspecified) given DMMPA (0.57 g/kg body weight by gavage) daily for 100-240 days, other than mild congestion in the lungs, sometimes coupled with a small number of hemorrhagic spots. At higher doses (0.9 g/kg), DMMPA damaged the lungs, liver, and kidneys and depressed the heart rate.

In reproductive toxicity tests, male and female rats (strain unspecified) were allowed to mate after receiving DMMPA orally at 200 µl per day for 100 days. The number of pregnancies, the average number of pups per litter, and the number of stillborn observed were similar to those in untreated controls. The first generation offspring from the dosed parents developed and reproduced normally. When dosed males were mated to untreated females or vice versa, the number of pregnancies, the average number of pups per litter, and the number of stillborn produced were also similar to those in untreated controls (Coleman, 1977b).

TABLE 1. PROPERTIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (a)

Empirical formula	$C_6H_{14}NO_4P$
Molecular weight	195.16
Melting point	17.6° C
Boiling point (3 mm)	108°-109° C
Specific gravity (20/20° C)	1.223 g/cc
Refractive index n_D (25° C)	1.4530
Vapor pressure (30° C)	0.01 mm Hg
Absolute viscosity (25° C)	0.158 stokes
Stability in water	
pH 4.88-6.63, 37° C	Stable 1 h
pH 2.52, 37° C	33% loss in 1 h
pH 2.37, 37° C	60% loss in 1 h
Stability in human urine under toluene 2°-5° C	Stable 6 months
Stability in desiccator 2°-5° C	Stable 5 months
Solubility	Soluble in water, propylene, glycol, benzene, ether, *n*-hexane
Available purity	>99%
Impurities	N-methylmorpholine Morpholine Trimethylphosphate Methyl chloride Morpholine analog of DMMPA Dimorpholine derivative of pyrophosphoric acid

(a) Arbuzov et al., 1964; McNally and Adie, 1977; Coleman, 1977a; Gray, A., Defence Research Establishment, personal communication to Dr. S. Olin, Tracor Jitco, Inc., 6/22/77; Dawson et al., 1978

DMMPA placed directly on the corneal surface of rabbits caused eye irritation and temporary damage to the conjunctiva and nictitating membrane but had no effect on intraocular pressure (Coleman, 1977a). The rabbits recovered from the damage to the conjunctiva and nictitating membrane in 24 hours.

DMMPA was absorbed readily through the skin of rats, very little (approximately 1%) DMMPA being recovered from the site of application 1 hour after topical application of 64 mg of neat DMMPA (Dawson et al., 1978). Degradation of DMMPA was not observed in human plasma incubated at 37° C for 3 days. The half-life in blood of DMMPA administered intravenously (5-50 mg/kg) to New Zealand rabbits was 43 minutes (Coleman, 1977a). DMMPA was a weak inhibitor of rat brain cholinesterase activity in vitro (concentration greater than 2.5×10^{-4} M required to produce 50% inhibition) (Jones et al., 1948), but DMMPA at 300 mg/kg administered by intravenous injection did not affect blood cholinesterase activity in New Zealand rabbits (time of blood sampling was not specified; A. Gray, Defence Research Establishment, personal communication to Dr. S. Olin, Tracor Jitco, Inc., 6/22/77).

When DMMPA at 2-200 mg was administered intraperitoneally to rats, 1% of the dose was recovered in the liver, 0.5% in the kidneys, and 0.5% in the brain 4 hours after administration; only trace amounts (less than 0.05%) were recovered in these tissues 24-48 hours later (Dawson et al., 1978). Retention of DMMPA in other organs was not studied. Fifty-eight percent of the intraperitoneally administered DMMPA in rats was recovered unchanged in the urine after 24 hours (Dawson et al., 1978), and 25% of the DMMPA administered orally or intramuscularly in humans was recovered unchanged in the urine after 48 hours (McNally and Adie, 1977). The amount of unchanged DMMPA recovered in the urine after topical application was 25% after 24 hours in rats (Dawson et al., 1978) and 15% after 48 hours in humans (McNally and Adie, 1977).

DMMPA was not mutagenic in strains TA100, TA1535, TA1537, or TA98 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or male Syrian hamster liver S9 (Appendix L, Table L1). However, DMMPA was mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma assay in the absence of S9; it was not tested in the presence of S9. The doses at which a positive response was obtained were over 2 mg/ml (Appendix L, Table L2). DMMPA also induced chromosomal aberrations and sister-chromatid exchanges in Chinese hamster ovary (CHO) cells in the absence of S9. Again a dose of 2 mg/ml was required to produce a positive response. Cytogenetic effects were not observed in the presence of Aroclor 1254-induced rat liver S9 (Appendix L, Tables L3 and L4). San (1984) reported positive effects of DMMPA on chromosomal aberrations, sister-chromatid exchanges, and micronuclei in CHO cells and DNA repair inhibition in diploid human skin fibroblasts. DMMPA was not mutagenic in three generations of *Drosophila melanogaster* (S. Lipnick, U.S. Army, Edgewood Arsenal, Aberdeen Proving Ground, Maryland, personal communication to J. Douglas, NCI, 9/9/76).

Study Rationale: DMMPA was selected for long-term toxicity and carcinogenicity study because of the potential for human exposure and the lack of toxicity data. The U.S. Army requested that the NCI/NTP conduct toxicity studies on DMMPA and three other nerve agent simulants: tris(2-ethylhexyl)phosphate (NTP, 1984), dimethyl hydrogen phosphite (NTP, 1985), and dimethyl methyl phosphonate. One of these compounds, dimethyl hydrogen phosphite, was hydrolyzed readily in water and had to be administered in corn oil. For comparative purposes, the four agents were administered in corn oil by the gavage route.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Test Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dimethyl morpholinophosphoramidate was obtained in three batches from the Defence Research Establishment, Suffield, Canada (Table 2). Purity, identity, and stability analyses were conducted at Midwest Research Institute (Appendix G). Results of elemental analyses of lot no. E112877 (batch 01) were in agreement with theoretical values. Results of elemental analyses of lot no. E112877 (batch 02) for phosphorus, nitrogen, and hydrogen were in agreement with theoretical values; those for carbon were slightly low (98.6%). Results of elemental analyses of lot no. D021381 for carbon, phosphorus, and hydrogen were in agreement with theoretical values; those for nitrogen were slightly high (106.89%). Results of thin-layer chromatography of lot no. E112877 (batch no. 01) indicated four trace impurities. Two minor, two trace, and two slight trace impurities in lot no. E112877 (batch 02) were detected by thin-layer chromatography. One minor, three trace, and two slight trace impurities in lot no. D021381 were detected by thin-layer chromatography. Seven impurities with a combined area of 0.48% that of the major peak were detected in lot no. E112877 (batch 01) by gas chromatography. Nine impurities with a combined area of 0.57% that of the major peak were detected in lot no. E112877 (batch 02) by gas chromatography. Ten impurities with a combined area of 0.64% that of the major peak were detected in lot no. D021381 by gas chromatography. Thus, the three batches of DMMPA used in the studies were approximately 99% pure.

For all three batches, the infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those expected for the structure and with the spectra supplied by the Defence Research Establishment, Suffield, Canada.

The bulk chemical was stable (as measured by gas chromatography) when stored for 2 weeks at temperatures ranging from −20° C to 60° C; however, discoloration of the 60° C sample indicated possible decomposition not measured by the analytical method. DMMPA was stored at the testing laboratory at −20° C. Periodic reanalyses of the bulk chemical at the testing laboratory by infrared spectroscopy and gas chromatography indicated that no deterioration of the chemical occurred over the course of the studies (Appendix G).

TABLE 2. IDENTITY AND SOURCE OF THE LOTS USED IN THE GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers Used	E112877 (batch 01)	E112877 (batch 01)	E112877 (batches 01 and 02); D021381
Date of Initial Use of Each Lot	E112877 (batch 01), 6/13/78	E112877 (batch 01), 10/16/78	E112877 (batch 01), 4/30/80; E112877 (batch 02), 10/22/80; D021381, 4/22/81
Supplier	Defence Research Establishment, Suffield, Canada	Same as 14-d studies	Same as 14-d studies

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

DMMPA and corn oil were mixed to give the desired concentrations (Table 3). DMMPA (10% w/v) in corn oil was found to be stable when stored at room temperature for 7 days (Appendix H). DMMPA/corn oil mixtures were stored at room temperature for no longer than 7 days. Formulations of DMMPA in corn oil were periodically selected at random and analyzed in duplicate by gas chromatography at the testing laboratory to estimate the accuracy with which formulations were prepared over the course of the studies (Appendix I). In addition, a split sample was sent to the analytical chemistry laboratory for referee analysis six times each year during the 2-year studies. Because 3/48 samples analyzed were not within 10% of the target concentrations, the dose solutions are estimated to have been prepared within specifications 94% of the time (Table 4; Appendix J, Table J2).

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	A known quantity of DMMPA was diluted with corn oil	Same as 14-d studies	DMMPA was pipetted into a graduated cylinder, diluted to required volume with corn oil, and thoroughly mixed by inversion
Maximum Storage Time	4 d	4 d	7 d
Storage Conditions	Room temperature	Room temperature	Room temperature

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Concentration of DMMPA in Corn Oil for Target Concentration (mg/ml)				
	45 mg/ml	90.1 mg/ml		180.2 mg/ml	
		Mouse	Rat	Mouse	Rat
Mean (mg/ml)	44.4	91.3	91.1	180.6	181.5
Standard deviation	1.96	4.18	4.22	16.69	15.80
Coefficient of variation (percent)	4.4	4.6	4.6	9.2	8.7
Range (mg/ml)	40.9-47.4	82.7-99.9	82.7-99.9	160.6-221.0	160.6-221.0
Number of samples	16	15	15	13	13

II. MATERIALS AND METHODS

FOURTEEN-DAY STUDIES

Three-week-old male and female F344/N rats and 6-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries (Indianapolis, Indiana) and held in quarantine for 2 weeks before the studies began. The animals were identified by ear cut and cage card. Groups of five rats of each sex were administered DMMPA in corn oil at doses of 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg body weight by gavage for 14 consecutive days. Groups of five mice of each sex were administered 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg on the same schedule. The dose volume was 4.1 ml/kg for rats and 3.3 ml/kg for mice. The doses were selected based on toxicity data from technical reports supplied by the Defence Research Establishment, Suffield, Canada (Coleman, 1977a,b). The purpose of the 14-day studies was to set doses for the 13-week studies.

Animals were housed five per cage and received water (acidified to pH 2.5 with hydrochloric acid to inhibit bacterial growth) and feed ad libitum. The rats and mice were observed once per day and were weighed on days 1 and 15 of the studies. Necropsies were performed on all animals. Further details of animal maintenance are presented in Table 5.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of DMMPA and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries, observed for 3 weeks (rats) or 17 days (mice) in quarantine, and then assigned to cages according to a table of computer-generated random numbers. The cages were then assigned to dosed and vehicle control groups according to another table of random numbers.

Groups of 9 or 10 rats and mice of each sex were administered DMMPA at doses of 0, 200, 400, 800, 1,200, or 1,600 mg/kg body weight in corn oil by gavage, 5 days per week for 13 weeks. The doses were selected based on mortality rates in the 14-day studies. Further experimental details are summarized in Table 5.

Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. Liver and lung weights were recorded for all survivors because Coleman (1977b) reported that DMMPA administration caused an increase in lung and liver weights. Necropsies were performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered DMMPA in corn oil by gavage at doses of 0, 150, 300, or 600 mg/kg body weight, 5 days per week for 103 weeks. Initially, all rat groups contained 50 animals; but during week 1, a rat in the mid dose female group was determined to be a male and was removed from the study. Groups of 50 male mice were administered 0, 150, or 300 mg/kg and groups of 50 female mice were administered 0, 300, or 600 mg/kg on the same schedule.

Source and Specifications of Test Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the testing laboratory at 4 weeks of age and mice at 5-6

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Test Groups	5 males and 5 females of each species	9 or 10 males and 10 females of each species	50 males and 49 or 50 females of each species
Doses	Rats--0, 313, 625, 1,250, 2,500, or 5,000 mg/kg DMMPA in corn oil by gavage; mice--0, 250, 500, 1,000, 2,000, or 4,000 mg/kg DMMPA in corn oil by gavage; 5,000 mg/kg dose given neat; dose vol--3.3 ml/kg (mice); 4.1 ml/kg (rats)	0, 200, 400, 800, 1,200, or 1,600 mg/kg DMMPA in corn oil by gavage; dose vol--10 ml/kg for rats and mice	Rats--0, 150, 300, or 600 mg/kg DMMPA in corn oil by gavage; male mice--0, 150, or 300 mg/kg; female mice--0, 300, or 600 mg/kg DMMPA in corn oil by gavage; dose vol--3.3 ml/kg for rats and mice
Date of First Dose	Rats--6/14/78; mice--6/13/78	10/16/78	Rats--4/30/80; mice--female: 5/14/80; male: 1/6/81
Date of Last Dose	Rats--6/27/78; mice--6/26/78	Rats--1/17/79; mice--1/15/79	Rats--4/23/82; mice--female: 5/10/82; male: 12/31/82
Duration of Dosing	14 d	5 d/wk for 13 wk	5d/wk for 103 wk
Type and Frequency of Observation	Observed daily; weighed on d 1 and 15	Observed 2 × d; clinical observations and body weights recorded 1 × wk	Observed 2 × d; palpated 1 × 4 wk; weighed 1 × wk for 13 wk and 1 × mo thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals	Necropsy performed on all animals; histologic exam performed on all animals in the vehicle control and the 1,600 mg/kg groups and on animals that died before the end of the studies; tissues examined: gross lesions and tissue masses, mandibular or mesenteric lymph nodes, salivary glands, sternebrae (including marrow), thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, lungs and mainstem bronchi, skin, heart, esophagus, stomach, brain, thymus, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, trachea; liver and lung weights recorded for all survivors	Necropsy performed on all animals; histologic exam performed on all animals; tissues examined include: gross lesions and tissue masses, blood smear, mandibular and mesenteric lymph nodes, salivary glands, sternebrae, (including marrow), thyroid gland, parathyroids, colon, liver, urinary bladder, prostate/testes/seminal vesicles or ovaries/uterus, lungs and mainstem bronchi, cecum, skin, gallbladder (mice), thigh muscle, costochrondral junction (rib), larynx, nasal cavity, heart, esophagus, stomach, brain, thymus, pancreas, spleen, kidneys, adrenal glands, pituitary gland, eyes, mammary gland, duodenum, ileum, sciatic nerve, rectum, jejunum
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; $B6C3F_1$ mice	Same as 14-d studies	Same as 14-d studies
Animal Source	Harlan Industries, Inc. (Indianapolis, IN)	Same as 14-d studies	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Charles River Breeding Laboratories (Kingston, NY)

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Testing Laboratory	Litton Bionetics, Inc.	Same as 14-d studies	Same as 14-d studies
Time Held Before Test	2 wk	Rats--3 wk; mice--17 d	2 wk
Age When Placed on Study	Rats--5 wk; mice--8 wk	7 wk	Rats--6 wk; mice--7-8 wk
Age When Killed	Rats--7 wk; mice--10 wk	20 wk	Rats--111 wk; mice--112-113 wk
Necropsy Dates	Rats--6/28/78; mice--6/27/78	Rats--1/18-1/19/79; mice--1/16-1/17/79	Rats--5/3/82-5/7/82; mice--female: 5/17/82-5/18/82; male: 1/10/83-1/11/83
Method of Animal Distribution	Assigned to groups so that average cage weights were approximately equal	Assigned to cages, then to groups according to a series of computer-generated random numbers	Same as 13-wk studies
Animal Identification	Ear cut and cage card	Same as 14-d studies	Ear tag (rats), ear punch (mice), toe clip, and cage card
Feed	Purina Lab Chow meal (Ralston Purina, St. Louis, MO); available ad libitum	Purina Lab Chow Pellets (Ralston Purina, St. Louis, MO); available ad libitum	NIH 07 Open formula (Zeigler Bros., Gardners, PA); available ad libitum
Bedding	Absorb-Dri® (Lab Products, Inc., Garfield, NJ)	Same as 14-d studies	Absorb-Dri®, heat-treated hardwood chips (Williams Feed and Bedding, Co., Gaithersburg, MD) and Sani-Chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)
Water	Acidified to pH 2.5 with HCl, available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ, and Hazleton Systems Aberdeen, MD)	Polycarbonate (Lab Products, Inc., Garfield, NJ)	Polycarbonate (Lab Products, Inc., Garfield, NJ, or Rochelle Park, NJ, and Hazleton Systems, Aberdeen, MD)
Cage Filters	Nonwoven filter paper (Snow Filtration Co., Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage	5	5	5
Other Chemicals on Test in the Same Room	Tris(2-ethylhexyl)phosphate	None	None
Animal Room Environment	Temp--23° ± 1° C; rel hum--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h	Same as 14-d studies	Temp--20°-27° C; rel hum--16%-98%; fluorescent light 12 h/d; 12-15 room air changes/h

weeks of age. The animals were quarantined at the testing facility for 2 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 6 weeks of age, and the mice, at 7-8 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci. The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the 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 randomly 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 these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage in polycarbonate cages. Feed and water (acidified to pH 2.5 with 0.1N hydrochloric acid) were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. Necropsies were performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

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. Tissues examined microscopically are listed in Table 5.

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 histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original

pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group.

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and the PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

Data Recording: 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, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not 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) life table test for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is 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 the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which necropsies were performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect 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. All reported P values for tumor analyses are one-sided.

Life Table Analyses--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 vehicle 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).

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the

terminal-kill period. The denominators of these proportions were the number of animals on which necropsies were actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent vehicle control group is always the first and most appropriate vehicle control group used for decisionmaking, there are certain instances in which historical control data can be helpful in the overall evaluation of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors in these studies appearing to show compound-related effects.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All male and female rats that received dimethyl morpholinophosphoramidate at 2,500 mg/kg, all female rats that received 5,000 mg/kg, and 4/5 male rats that received 5,000 mk/kg died before the end of the studies (Table 6). The final mean body weights of male and female rats that received 1,250 mg/kg were approximately 8% lower than that of the vehicle controls. At lower doses, the effects of DMMPA on body weight did not follow a dose-related pattern. Necropsies were performed on all animals. Compound-related gross lesions were not observed. Tissues were not examined microscopically. Based on the toxicity and survival data, 1,600 mg/kg was selected as the highest dose for the 13-week studies.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change	
MALE					
0	5/5	112	151	+ 39	--
313	5/5	112	155	+ 43	102.6
625	5/5	112	163	+ 51	107.9
1,250	5/5	112	140	+ 28	92.7
2,500	(c) 0/5	113	(d)	(d)	(d)
5,000	(e) 1/5	113	157	+ 44	104.0
FEMALE					
0	5/5	94	115	+ 21	--
313	5/5	91	111	+ 20	96.5
625	5/5	95	111	+ 16	96.5
1,250	5/5	93	106	+ 13	92.2
2,500	(f) 0/5	92	(d)	(d)	(d)
5,000	(g) 0/5	94	(d)	(d)	(d)

(a) Number surviving/number in group
(b) Initial group body weight
(c) All deaths were on day 3.
(d) All animals died before the end of the studies.
(e) Day of death: 2,3,3,5
(f) Day of death: 1,2,3,3,3
(g) Day of death: 2,2,2,2,4

THIRTEEN-WEEK STUDIES

The following animals died during the studies: 1/10 males that received 800 mg/kg, 3/10 males and 2/10 females that received 1,200 mg/kg, and 1/10 males and 1/10 females that received 1,600 mg/kg (Table 7). The death of a male rat during week 1 in the 1,200 mg/kg group was attributed to gavage injury. Dosed male rats gained more weight than did the vehicle controls. Final mean body weights of female rats were not dose related. Both male and female vehicle controls lost weight between weeks 1 and 2, whereas dosed rats gained approximately 20 g. Malfunctioning of the automatic watering system in one cage in each of the vehicle control male and female groups may have been responsible for the weight loss.

Absolute and relative liver weights of dosed rats of each sex were greater than those of the vehicle controls; the increase was dose related (Table 8). Compound-related gross or microscopic pathologic lesions and effects on lung weight were not observed.

Dose Selection Rationale: Based on the toxicity, liver weight, and survival data, doses selected for rats for the 2-year studies were 0, 150, 300, or 600 mg DMMPA/kg body weight in corn oil, to be administered 5 days per week by gavage.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change	
MALE					
0	10/10	131	258	+ 127	--
200	10/10	134	286	+ 152	110.9
400	10/10	132	274	+ 142	106.2
800	(c) 9/10	135	282	+ 147	109.3
1,200	(d) 7/10	128	285	+ 157	110.5
1,600	(e) 9/10	130	275	+ 145	106.6
FEMALE					
0	10/10	105	179	+ 74	--
200	10/10	104	175	+ 71	97.8
400	10/10	101	169	+ 68	94.6
800	10/10	109	180	+ 71	100.6
1,200	(f) 8/10	103	169	+ 66	94.4
1,600	(g) 9/10	107	176	+ 69	98.3

(a) Number surviving/number in group
(b) Initial group body weight
(c) Week of death: 11
(d) Week of death: 1,13,13
(e) Week of death: 8
(f) Week of death: 10,11
(g) Week of death: 13

TABLE 8. BODY, LIVER, AND LUNG WEIGHTS IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dose (mg/kg)	No. Examined	Weight at Necropsy (grams)	Liver Weight (grams)	Lung Weight (grams)	Relative Organ Weight	
					Liver/Body (mg/kg)	Lung/Body (mg/kg)
MALE						
0	10	(a) 255.7 ± 26.5	7.98 ± 0.69	1.25 ± 0.18	(a) 31.8 ± 4.27	(a) 4.8 ± 0.62
200	10	(b) 288.6 ± 19.2	(b) 10.60 ± 1.75	1.38 ± 0.17	36.6 ± 4.59	4.8 ± 0.52
400	10	268.4 ± 17.4	(b) 10.69 ± 1.89	1.40 ± 0.27	(b) 39.8 ± 6.38	5.2 ± 0.96
800	9	270.1 ± 32.0	(b) 11.86 ± 1.06	1.43 ± 0.39	(b) 44.3 ± 4.67	5.4 ± 1.50
1,200	7	281.3 ± 25.2	(b) 12.34 ± 1.29	1.34 ± 0.15	(b) 43.9 ± 2.41	4.8 ± 0.28
1,600	9	266.4 ± 10.9	(b,c) 12.86 ± 1.23	1.37 ± 0.17	(b,c) 48.7 ± 5.28	5.1 ± 0.63
FEMALE						
0	10	166.8 ± 11.4	4.87 ± 0.71	0.98 ± 0.12	29.2 ± 3.94	5.9 ± 0.76
200	10	173.1 ± 17.1	(b) 6.06 ± 0.83	(d) 1.10 ± 0.31	(b) 35.1 ± 3.87	(d) 6.4 ± 0.19
400	10	164.5 ± 14.8	(b) 5.97 ± 0.79	0.93 ± 0.10	(b) 36.4 ± 4.73	5.6 ± 0.59
800	10	175.6 ± 14.5	(b) 6.70 ± 0.60	1.11 ± 0.13	(b) 38.2 ± 2.91	6.3 ± 0.55
1,200	8	162.0 ± 12.8	(b) 6.43 ± 0.96	1.01 ± 0.11	(b) 39.7 ± 5.23	6.3 ± 0.73
1,600	9	166.3 ± 12.6	(b) 7.18 ± 0.96	1.13 ± 0.22	(b) 43.1 ± 4.29	6.8 ± 1.13

(a) Data from nine values (mean ± standard deviation). One body weight not taken.
(b) $P<0.01$, Dunnett's test (Miller, 1981)
(c) One liver weight was judged to be in error and was not included in the calculations.
(d) One lung weight was judged to be in error and was not included in the calculations.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of mid dose and high dose male rats were slightly lower than those of the vehicle controls throughout most of the studies (Table 9 and Figure 1). The mean body weights of high dose female rats were slightly lower than those of the vehicle controls after week 32.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Weeks on Study	Control (Veh)		150 mg/kg			300 mg/kg			600 mg/kg		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent veh cont)	No. of Survivors	Av Wt (grams)	Wt (percent veh cont)	No. of Survivors	Av Wt (grams)	Wt (percent veh cont)	No. of Survivors
MALE											
0	133	50	141	106	50	133	100	50	139	105	50
1	168	50	174	104	50	166	99	50	171	102	50
2	203	50	209	103	50	198	98	50	204	100	50
3	227	50	231	102	50	223	98	50	230	101	50
4	250	50	251	100	50	244	98	50	249	100	50
5	257	50	258	100	50	253	98	50	256	100	50
6	276	50	276	100	50	269	97	50	271	98	50
7	284	50	286	101	50	276	97	50	274	96	50
8	302	50	297	98	50	290	96	50	290	96	50
9	308	50	306	99	50	296	96	50	295	96	50
10	316	50	315	100	50	309	98	50	305	97	50
11	324	50	323	100	50	320	99	50	316	98	50
12	331	50	331	100	50	325	98	50	319	96	50
13	341	50	341	100	50	334	98	50	329	96	50
16	351	50	359	102	50	344	98	50	336	96	50
20	367	50	368	100	50	361	98	50	350	95	50
24	383	50	390	102	50	379	99	50	367	96	50
28	392	50	402	103	50	389	99	50	376	96	50
32	415	50	419	101	50	404	97	50	388	93	50
36	429	50	439	102	50	425	99	50	403	94	50
40	444	50	451	102	50	432	97	50	413	93	49
44	447	50	455	102	50	437	98	50	412	92	49
48	465	50	470	101	50	450	97	50	431	93	49
52	467	50	478	102	50	458	98	50	436	93	49
56	476	50	476	100	50	451	95	50	427	90	49
60	482	50	486	101	50	463	96	49	439	91	48
64	490	50	487	99	49	465	95	49	444	91	48
68	491	50	491	100	48	470	96	48	446	91	47
72	489	49	486	99	48	472	97	47	446	91	46
76	489	49	490	100	48	474	97	46	451	92	46
80	491	46	486	99	46	472	96	45	449	91	46
84	494	45	485	98	46	469	95	45	450	91	44
88	482	44	481	100	43	465	96	43	445	92	40
92	480	42	475	99	41	457	95	39	439	91	39
96	476	39	464	97	40	450	95	33	437	92	34
100	470	38	461	98	40	445	95	32	426	91	30
104	467	38	448	96	38	448	96	30	427	91	23
FEMALE											
0	107	50	106	99	50	106	99	49	106	99	50
1	123	50	121	98	50	123	100	49	121	98	50
2	138	50	138	100	50	139	101	49	136	99	50
3	146	50	147	101	50	150	103	49	148	101	50
4	157	50	158	101	50	161	103	49	158	101	50
5	161	50	162	101	50	166	103	49	162	101	50
6	168	50	169	101	50	172	102	49	169	101	50
7	175	50	175	100	50	177	101	49	174	99	50
8	181	50	180	99	50	182	101	49	178	98	50
9	183	50	182	99	50	185	101	49	182	99	50
10	188	50	188	100	50	190	101	49	187	99	50
11	190	50	192	101	50	193	102	49	192	101	50
12	194	50	193	99	50	195	101	49	191	98	50
13	196	50	195	99	50	197	101	49	194	99	50
16	204	50	201	99	50	201	99	49	198	97	50
20	205	50	204	100	50	204	100	49	201	98	50
24	211	50	207	98	50	209	99	49	208	99	50
28	214	50	211	99	50	212	99	49	209	98	50
32	224	50	217	97	49	217	97	49	213	95	50
36	231	50	223	97	49	226	98	48	218	94	48
40	237	50	228	96	49	228	96	47	222	94	46
44	238	50	230	97	49	232	97	47	225	95	45
48	247	50	240	97	49	239	97	47	231	94	45
52	253	50	244	96	49	241	95	47	233	92	45
56	263	50	247	94	49	249	95	46	239	91	45
60	271	50	261	96	49	264	97	46	248	92	45
64	283	49	269	95	49	274	97	46	255	90	44
68	289	49	278	96	46	285	99	46	263	91	43
72	293	49	286	98	45	297	101	43	274	94	43
76	302	48	292	97	45	303	100	43	279	92	43
80	305	48	295	97	44	307	101	43	284	93	40
84	308	45	297	96	44	308	100	43	286	93	37
88	309	44	298	96	42	310	100	42	283	92	37
92	302	44	299	99	41	312	103	42	285	94	35
96	304	42	297	98	39	308	101	39	287	94	32
100	306	41	308	101	35	312	102	38	292	95	27
104	308	38	309	100	35	318	103	33	298	97	25

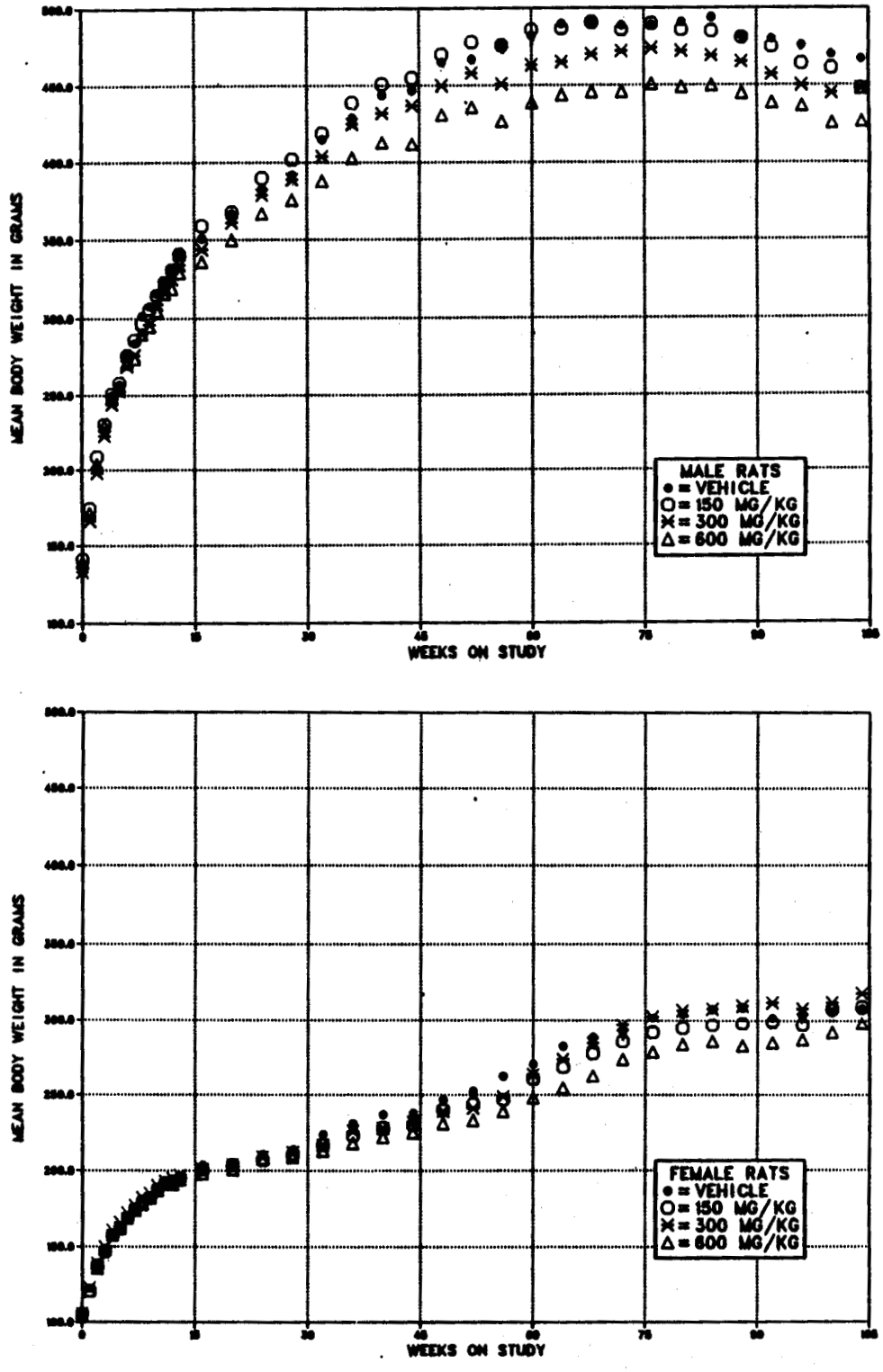


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats administered DMMPA at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The high dose groups of both male and female rats had significantly lower survival than did the vehicle controls, and the survival of mid dose male rats was marginally reduced (Table 10). For males, the survival of the high dose group was significantly lower than that of the vehicle controls after week 103; for females, the survival was significantly lower after week 91. The deaths of five animals with lung congestion before week 40 probably was a factor in the overall low survival of the high dose female group.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions in the hematopoietic system, skin, urinary system, liver, and pituitary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix E, Tables E1 and E2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	12	12	22	26
Accidentally killed	0	0	0	1
Killed at termination	37	37	28	22
Died during termination period	1	1	0	1
Survival P values (c)	0.002	0.972	0.066	0.011
FEMALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	14	15	13	25
Accidentally killed	0	0	3	0
Animals missexed	0	0	1	0
Killed at termination	36	35	33	24
Died during termination period	0	0	0	1
Survival P values (c)	0.010	0.860	0.996	0.021

(a) Terminal kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

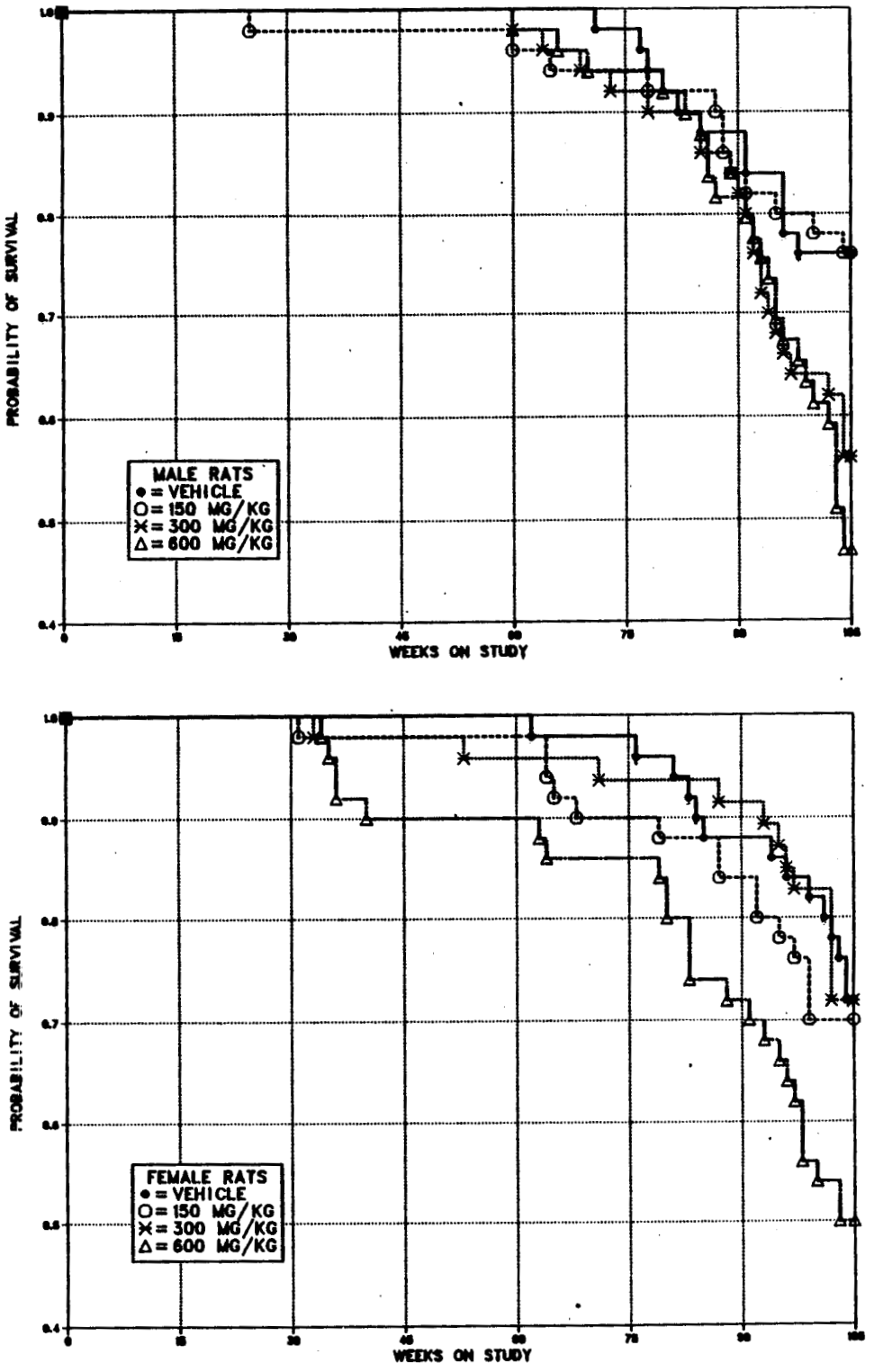


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with a significant positive trend, and the incidences in the high dose groups were significantly greater than those in the vehicle controls (Table 11). This hematopoietic neoplasm was recognized in its earliest stage as a diffuse infiltration of atypical mononuclear cells in the sinusoids of the liver and the interfollicular pulp of the spleen. In more advanced cases, there were infiltrations into virtually all organs and tissues. One high dose male also developed malignant lymphoma.

The diagnoses of mononuclear cell leukemia were classified according to the extent of the disease as stage 1 (early), stage 2 (intermediate), or stage 3 (advanced). The criteria used are described on the following page.

TABLE 11. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (a)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
MALE				
Mononuclear Cell Leukemia (b)				
Overall Rates	14/50 (28%)	21/50 (42%)	19/50 (38%)	25/50 (50%)
Adjusted Rates	30.7%	49.6%	47.3%	63.4%
Terminal Rates	7/38 (18%)	17/38 (45%)	8/28 (29%)	10/23 (43%)
Life Table Tests	P=0.001	P=0.123	P=0.088	P=0.003
Incidental Tumor Tests	P=0.127	P=0.082	P=0.440	P=0.127
FEMALE				
Mononuclear Cell Leukemia (c)				
Overall Rates	9/50 (18%)	13/50 (26%)	12/49 (24%)	18/50 (36%)
Adjusted Rates	20.1%	32.0%	29.5%	49.5%
Terminal Rates	3/36 (8%)	8/35 (23%)	6/33 (18%)	7/25 (28%)
Life Table Tests	P=0.005	P=0.215	P=0.259	P=0.008
Incidental Tumor Tests	P=0.063	P=0.196	P=0.284	P=0.051

(a) The statistical methods used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at testing laboratory (mean ± SD): 17.3% ± 11.7%; historical incidence in NTP studies: 12.2% ± 7.6%
(c) Historical incidence at testing laboratory (mean ± SD): 29.3% ± 13.0%; historical incidence in NTP studies: 16.1% ± 8.9%

Stage 1--Spleen not enlarged or only moderately enlarged with few suspicious cells surrounding malpighian corpuscles of the spleen and only very few neoplastic cells in the liver sinusoids. No identifiable neoplastic cells in the blood vessels of the lung.

Stage 2--More severe than in the first category: spleen and/or liver only moderately enlarged with neoplastic cells in the liver sinusoids and the blood vessels of other organs.

Stage 3--Enlarged spleen and liver with many neoplastic cells in the liver sinusoids and the blood vessels of other organs.

According to these criteria, a greater number of stage 3 mononuclear cell leukemias were found in the dosed animals than in the vehicle controls. In male rats, 11 more diagnoses of mononuclear cell leukemia were made in the high dose group than in the vehicle control group, and 11 more lesions were judged as stage 3 in the high dose group than in the vehicle controls. In females, nine more diagnoses were made in the high dose group than in the vehicle controls, and seven more lesions were judged as stage 3 in the high dose group (Table 12).

TABLE 12. CLASSIFICATION OF MONONUCLEAR CELL LEUKEMIA INDUCED IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Total No. of Mononuclear Cell Leukemias	Stages		
		1	2	3
MALE				
Vehicle Control	14	2	2	10
Low Dose	21	5	10	6
Mid Dose	19	5	3	11
High Dose	25	1	3	21
FEMALE				
Vehicle Control	9	1	2	6
Low Dose	13	4	1	8
Mid Dose	12	2	0	10
High Dose	18	3	2	13

Skin: The incidences of squamous cell papillomas in male rats were significant by the trend tests; the increased incidence in the high dose group was not significantly greater than that in the vehicle controls by pairwise comparison (vehicle control, 1/50, 2%; low dose, 1/50, 2%; mid dose, 1/50, 2%; high dose, 4/50, 8%). Squamous cell papillomas of the integumentary system were not diagnosed in any female rat.

Urinary System: Mineralization of the renal papilla was observed at increased incidences in dosed male rats, particularly in the low dose group (male: vehicle control, 0/50; low dose, 23/50, 46%; mid dose, 5/50, 10%; high dose, 3/50, 6%; female: vehicle control, 0/50; low dose, 0/50; mid dose, 2/49, 4%; high dose, 1/50, 2%). This lesion consisted of accumulations of mineral crystals within renal papillary tubules and, to a lesser extent, deposition of mineral particles on the interstitial tissue of the renal papilla. A transitional cell carcinoma of the kidney was diagnosed in 1/50 high dose male rats; a transitional cell papilloma of the urinary bladder was diagnosed in 1/49 mid dose male rats and 1/49 vehicle control female rats.

Liver: Angiectasis was observed at increased incidences in dosed male rats (male: vehicle control, 1/50, 2%; low dose, 7/50, 14%; mid dose, 9/50, 18%; high dose, 14/50, 28%). The lesions consisted of small foci, usually subcapsular, in which the sinusoids were dilated and filled with blood. This lesion was not observed at increased incidence in the dosed female rats.

An increased incidence of neoplastic nodules in the liver of dosed male rats was seen (vehicle control, 1/50; low dose, 3/50; mid dose, 3/50; high dose, 3/50); none of the incidences was statistically significant.

Pituitary Gland: Adenomas of the pituitary gland in male rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls by pairwise comparison (Table 13). These lesions were often large enough to be observed grossly and consisted of sheets of small to large, round or ovoid cells supported by a delicate fibrovascular stroma. The larger adenomas commonly compressed and displaced the ventral aspect of the brain, particularly the brain stem in the region of the thalamus. Invasion of the brain, which was noted in one low dose female, was considered evidence of malignancy, and such neoplasms were classified as carcinomas.

TABLE 13. ANALYSIS OF PITUITARY GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Adenoma				
Overall Rates	7/50 (14%)	4/50 (8%)	7/48 (15%)	0/50 (0%)
Adjusted Rates	16.9%	10.5%	20.5%	0.0%
Terminal Rates	5/38 (13%)	4/38 (11%)	3/27 (11%)	0/23 (0%)
Life Table Tests	P=0.071N	P=0.264N	P=0.425	P=0.030N
Incidental Tumor Tests	P=0.018N	P=0.262N	P=0.574N	P=0.017N

FOURTEEN-DAY STUDIES

All mice that received 2,000 or 4,000 mg/kg DMMPA died before the end of the studies (Table 14). Final mean body weights were greater in the surviving groups of dosed mice than in the vehicle controls; the vehicle control mice did not gain weight during the study. Gross lesions were not observed in the dosed mice.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change	
MALE					
0	5/5	21	21	0	--
250	5/5	21	23	+ 2	109.5
500	5/5	20	23	+ 3	109.5
1,000	5/5	21	24	+ 3	114.3
2,000	(c) 0/5	21	(d)	(d)	(d)
4,000	(e) 0/5	21	(d)	(d)	(d)
FEMALE					
0	5/5	18	18	0	--
250	5/5	18	19	+ 1	105.6
500	5/5	18	19	+ 1	105.6
1,000	5/5	18	19	+ 1	105.6
2,000	(f) 0/5	18	(d)	(d)	(d)
4,000	(e) 0/5	18	(d)	(d)	(d)

(a) Number surviving/number in group
(b) Initial group body weight
(c) Day of death: 1,1,2,2,2
(d) All animals died before the end of the studies.
(e) Day of death: 1,1,2,3,4
(f) Day of death: 2,2,3,3,3

THIRTEEN-WEEK STUDIES

All males and 9/10 females that received 1,600 mg/kg died before the end of the studies (Table 15). The three deaths in the vehicle control group of male mice and six of the deaths in various dosed groups were due to gavage injury. There were no dose-related changes in mean body weights and relative liver and lung weights of male and female mice (Table 16). Problems with the automatic watering system occurred during week 1 in the 200 and 400 mg/kg groups of female mice and during week 4 in the 200 mg/kg group of female and 800 mg/kg group of male mice. Although the water cutoff caused a reduction in body weight of the animals initially, the final body weights (at 13 weeks) were not affected. Chemically related gross or microscopic pathologic effects were not observed.

Dose Selection Rationale: Based on the survival of mice in the 13-week studies, the doses of DMMPA selected for the mice in the 2-year studies were 0, 300, or 600 mg/kg. In the 2-year studies, however, 19 male mice in the 600 mg/kg group died by week 19. The cause of death was thought to be related to the toxic effects of DMMPA. Histopathologic investigation revealed congested lungs and adrenal glands. Consequently, all male mice were killed and the study restarted at doses of 0, 150, or 300 mg/kg. The action was taken because adding a 150 mg/kg group and a new vehicle control group while keeping the original 300 mg/kg and the original vehicle control group would have been more costly. Because very few early deaths occurred in the dosed female mice, that study was not restarted at lower doses.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change	
MALE					
0	6/9	22	29	+ 7	--
200	10/10	24	30	+ 6	103.4
400	8/10	22	31	+ 9	106.9
800	6/10	22	31	+ 9	106.9
1,200	3/10	25	29	+ 4	100
1,600	0/10	24	(c)	(c)	(c)
FEMALE					
0	10/10	20	24	+ 4	--
200	8/10	19	24	+ 5	100
400	10/10	19	24	+ 5	100
800	9/10	19	24	+ 5	100
1,200	9/10	19	24	+ 5	100
1,600	1/10	19	25	+ 6	104.2

(a) Number surviving/number in group
(b) Initial group body weight.
(c) All animals died before the end of the studies.

TABLE 16. LIVER AND LUNG WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (a)

Dose (mg/kg)	No. Examined	Liver (grams)	Lungs (grams)	Liver/Body Weight (percent)	Lung/Body Weight (percent)
MALE					
0	6	1.38 ± 0.31	0.246 ± 0.045	4.83 ± 0.58	0.87 ± 0.19
200	10	1.56 ± 0.27	0.232 ± 0.055	5.15 ± 0.55	0.78 ± 0.23
400	8	1.53 ± 0.24	0.224 ± 0.066	5.00 ± 0.57	0.73 ± 0.18
800	6	1.38 ± 0.23	0.206 ± 0.003	4.63 ± 0.36	0.70 ± 0.07
1,200	3	1.48 ± 0.23	0.216 ± 0.025	4.99 ± 0.22	0.73 ± 0.09
1,600	0	--	--	--	--
FEMALE					
0	10	1.09 ± 0.20	0.201 ± 0.044	4.67 ± 0.54	0.86 ± 0.17
200	8	1.17 ± 0.08	0.203 ± 0.039	5.04 ± 0.26	0.87 ± 0.17
400	10	1.14 ± 0.10	0.187 ± 0.044	4.85 ± 0.21	0.79 ± 0.19
800	9	1.17 ± 0.21	0.259 ± 0.186	4.98 ± 0.44	1.07 ± 0.58
1,200	9	1.08 ± 0.21	0.209 ± 0.045	4.66 ± 0.58	0.90 ± 0.15
1,600	(b) 1	1.01	0.236	4.40	1.03

(a) No statistically significant differences were observed between any dosed group and the vehicle controls (Dunnett's test).
(b) Not included in statistical calculations

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were comparable throughout the studies (Table 17 and Figure 3). Mean body weights of dosed female mice were slightly lower than those of the vehicle controls between weeks 24 and 72, but by week 88 and thereafter, the body weights of the dosed female mice and the vehicle controls were comparable.

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Weeks on Study	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent veh controls)	No. of Survivors	Av Wt (grams)	Wt (percent veh controls)	No. of Survivors
MALE	**Vehicle Control**			**150 mg/kg**			**300 mg/kg**	
0	23.6	50	23.1	98	50	23.7	100	50
1	25.2	50	24.9	99	50	25.3	100	50
2	26.8	50	27.0	101	50	26.5	99	50
3	27.4	50	27.1	99	50	27.6	101	50
4	29.0	50	28.5	98	50	28.8	99	50
5	29.2	50	29.1	100	50	29.1	100	48
6	30.5	50	30.3	99	50	30.4	100	47
7	30.4	50	30.0	99	50	30.3	100	47
8	31.1	50	30.9	99	50	30.9	99	47
9	32.1	50	31.5	98	50	31.9	99	47
10	31.8	50	31.5	99	50	31.9	100	47
11	31.9	50	31.8	100	50	31.5	99	47
12	33.2	50	32.9	99	50	33.1	100	47
13	32.6	50	32.6	100	50	32.5	100	47
16	34.1	50	33.7	99	50	33.9	99	47
20	35.0	50	35.1	100	50	34.9	100	47
24	36.0	50	36.2	101	50	35.9	100	47
28	38.1	50	38.0	100	50	37.7	99	47
32	38.9	50	38.5	99	50	39.0	100	46
36	39.7	50	38.8	98	49	39.3	99	46
40	39.3	50	38.9	99	49	39.9	102	46
44	40.2	50	39.6	99	49	40.3	100	46
48	39.5	49	39.2	99	49	39.9	101	46
52	39.4	49	39.4	100	49	40.0	102	46
56	39.3	49	39.4	100	49	40.1	102	46
60	39.9	49	40.0	100	49	40.0	100	45
64	38.4	49	39.1	102	49	39.3	102	45
68	39.5	49	39.9	101	49	39.8	101	45
72	40.1	48	40.7	101	49	41.1	102	45
76	39.7	48	40.7	103	49	40.0	101	45
80	39.9	48	41.2	103	48	41.2	103	45
84	39.4	47	40.5	103	47	40.9	104	45
88	40.0	45	41.0	103	46	41.4	104	45
92	40.2	43	41.0	102	44	40.7	101	44
96	39.8	42	40.4	102	41	40.6	102	43
100	40.3	41	40.9	101	37	41.0	102	41
104	39.5	41	40.2	102	37	40.0	101	39
FEMALE	**Vehicle Control**			**300 mg/kg**			**600 mg/kg**	
0	19.8	50	19.4	98	50	19.1	96	50
1	19.8	50	19.8	100	50	19.5	98	50
2	20.6	50	21.1	102	47	20.3	99	49
3	21.6	50	21.6	100	47	21.6	100	49
4	22.5	50	22.4	100	47	22.2	99	49
5	23.0	50	23.1	100	47	23.0	100	49
6	24.0	50	24.3	101	47	24.5	102	49
7	24.1	50	24.4	101	47	23.9	99	49
8	24.4	50	24.1	99	47	25.1	103	49
9	25.0	50	24.6	98	47	24.9	100	48
10	25.5	50	25.0	98	47	25.0	98	48
11	25.3	50	25.3	100	47	24.5	97	48
12	27.0	50	26.7	99	47	25.5	94	48
13	26.7	50	26.6	100	47	26.5	99	48
16	27.3	50	27.3	100	47	26.5	97	48
20	28.0	50	27.6	99	47	26.9	96	47
24	30.0	50	28.9	96	47	28.2	94	45
28	30.5	50	28.4	93	47	28.7	94	44
32	30.7	50	29.3	95	47	29.4	96	44
36	31.8	50	30.8	97	47	30.4	96	43
40	33.0	50	31.4	95	47	32.4	98	43
44	34.2	50	31.6	92	47	33.1	97	43
48	35.2	50	31.7	90	47	33.3	95	43
52	36.0	49	33.2	92	47	34.2	95	43
56	36.3	49	34.0	94	47	35.5	98	43
60	39.9	49	37.1	93	47	37.9	95	42
64	42.7	49	39.6	93	47	39.9	93	42
68	42.8	49	38.6	90	45	39.2	92	42
72	41.7	49	38.3	92	45	39.4	94	41
76	40.9	48	38.1	93	44	39.5	97	40
80	40.4	47	38.0	94	44	39.2	97	39
84	40.6	46	38.0	94	44	38.9	96	39
88	38.9	46	38.0	98	43	39.1	101	38
92	37.9	44	36.8	97	42	37.4	99	38
96	36.2	44	35.6	98	41	37.2	103	37
100	36.4	43	35.8	98	40	36.9	101	36
104	37.2	41	35.3	95	39	37.6	101	34

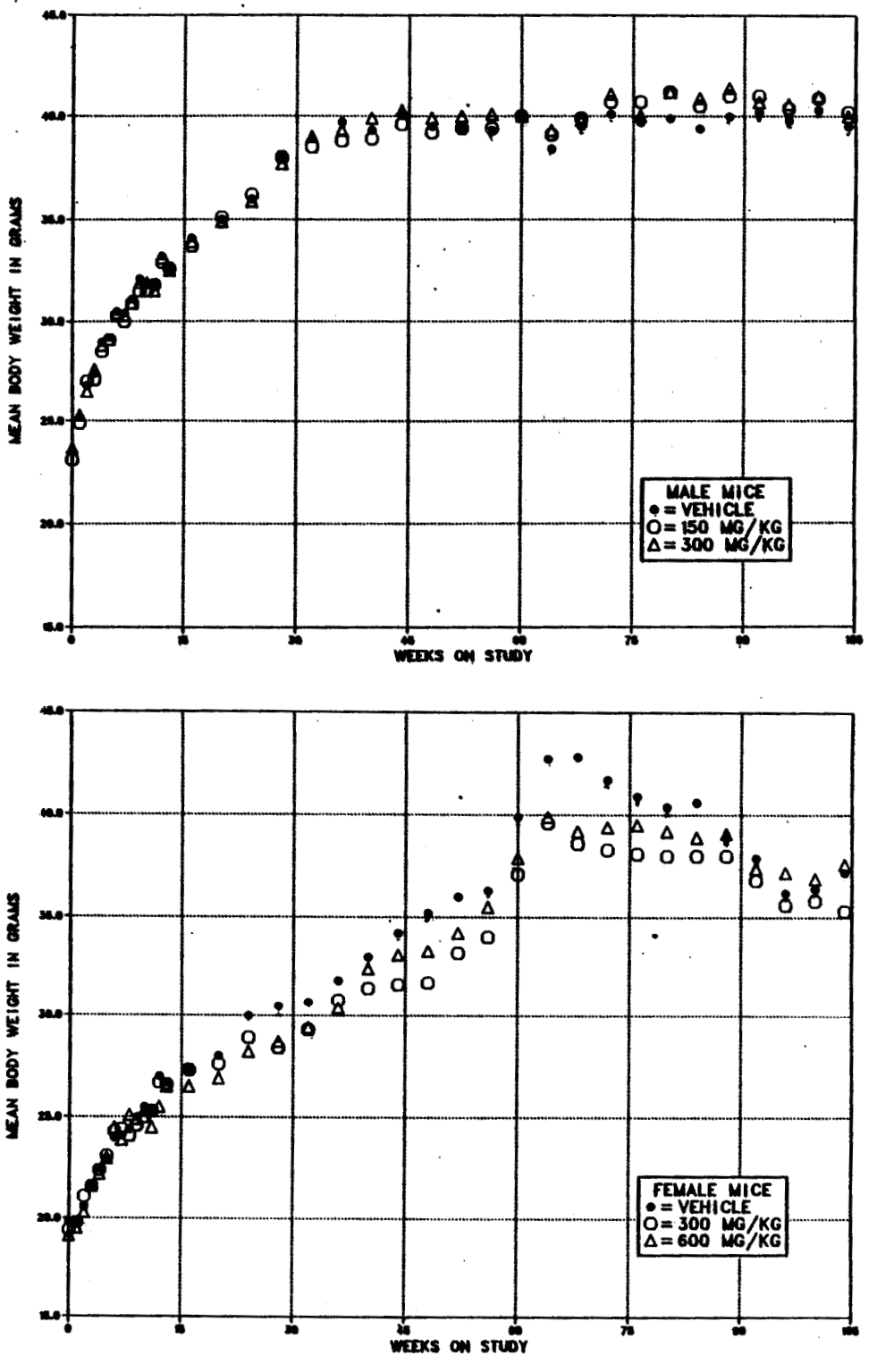


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice administered DMMPA at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. Six high dose female mice died by week 35 with congested lungs. The marginally significant (P=0.048) trend for female mice was primarily due to the early deaths in the high dose group (Table 18).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions in the stomach and liver. Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix E, Tables E3 and E4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

MALE (a)	Vehicle Control	150 mg/kg	300 mg/kg
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	14	11
Killed at termination	41	35	39
Died during termination period	0	1	0
Survival P values (c)	0.734	0.395	0.796
FEMALE (a)	**Vehicle Control**	**300 mg/kg**	**600 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	8	8	16
Accidentally killed	1	0	0
Animals missing	0	(d) 3	0
Killed at termination	41	39	34
Survival P values (c)	0.048	0.896	0.075

(a) Terminal kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(d) Three mice in one cage could not be accounted for at week 2 of the study.

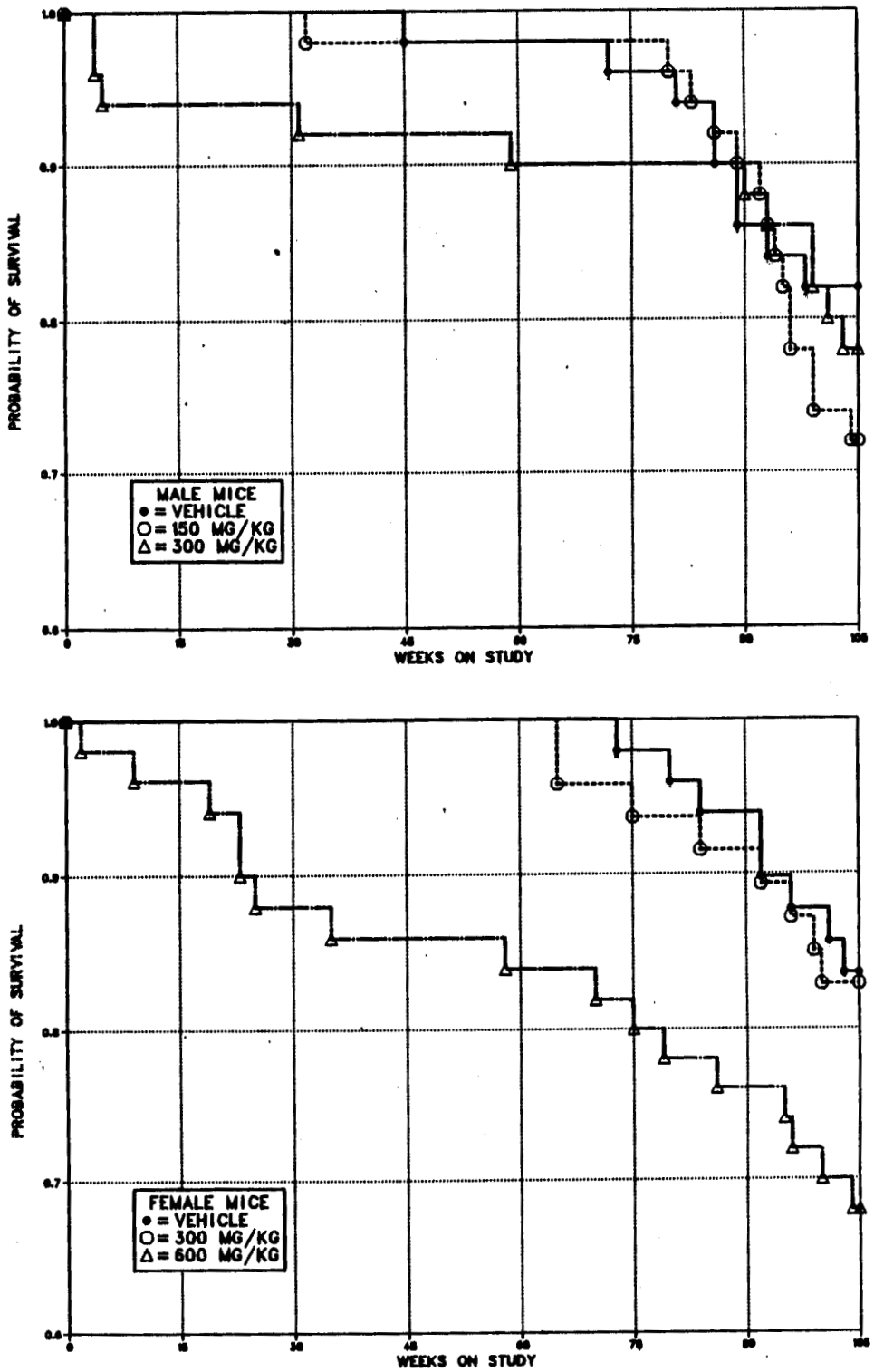


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Stomach: A squamous cell carcinoma was diagnosed in 1/47 low dose female mice; squamous cell papillomas were diagnosed in 1/46 high dose female mice and 2/50 low dose male mice.

Liver: Hepatocellular carcinomas in male mice occurred with a significant positive trend (P=0.032), but the incidence in the high dose group was not significantly greater than that in the vehicle controls (vehicle control, 6/50, 12%; low dose, 6/50, 12%; high dose, 12/50, 24%). The incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice were not significantly different from that in the vehicle controls (vehicle control, 11/50, 22%; low dose, 13/50, 26%; high dose, 15/50, 30%). The incidences of hepatocellular adenomas or carcinomas (combined) in dosed female mice were also not significantly different from that in the vehicle controls (vehicle control, 7/50, 14%; low dose, 4/47, 9%; high dose, 2/49, 4%).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Fourteen-day and 13-week studies were conducted with F344/N rats and B6C3F$_1$ mice to characterize DMMPA toxicity and to aid in selecting the doses for the 2-year studies.

In the 14-day studies, male and female rats were given DMMPA in corn oil by gavage at doses of 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg body weight for 14 consecutive days. All the animals in the two highest dose groups, except one male rat receiving 5,000 mg/kg, died within 5 days, and final mean body weights of males and females administered 1,250 mg/kg were marginally lower than those of the vehicle controls. Male and female mice were given doses of 0, 250, 500, 1,000, or 4,000 mg/kg for 14 days; all the animals in the two highest dose groups died. Final mean body weights of dosed mice were greater than those of the vehicle controls. Compound-related gross lesions were not found at necropsy in either the rats or mice. No histopathologic diagnoses were performed.

Rats and mice in the 13-week studies received doses of 0, 200, 400, 800, 1,200, or 1,600 mg/kg body weight. In rats, survival and weight gain were not affected by administration of DMMPA. Absolute and relative liver weights of dosed male and female rats were greater than those of the vehicle controls, but no compound-related gross or microscopic pathologic lesions were observed. All 10 male and 9/10 female mice administered 1,600 mg/kg died. Mean body weights were not affected by dosing, and no compound-related pathologic effects were seen in the other dosed groups.

In the 2-year studies, male and female rats received 0, 150, 300, or 600 mg/kg; male mice, 0, 150, or 300 mg/kg; and female mice, 0, 300, or 600 mg/kg. The doses were selected based on the liver weights and the survival of the rats and mice in the 13-week studies. Doses of 300 or 600 mg/kg were originally selected for male mice for the 2-year study; because 19/50 high dose male mice died by week 19, the male mice were killed and subsequently doses of 0, 150, and 300 mg/kg were selected for the restart of the 2-year study in male mice. In the 2-year studies, high dose male and female rats had slightly lower mean body weights and reduced survival relative to that of the vehicle controls; the mid dose male rats had a marginally lower survival rate.

The lower survival may be related to the early appearance and increased occurrence of mononuclear cell leukemia, which is fatal within 2 to 6 weeks after onset (Stromberg and Vogtsberger, 1983). However, the early deaths of five high dose female rats also contributed to the overall low survival of the group. The cause of these deaths is unknown.

There were positive trends for mononuclear cell leukemia in the dosed male and female rats. In the 600 mg/kg groups, both male and female rats had increased incidences of mononuclear cell leukemia compared with those of the vehicle controls. The incidences of mononuclear cell leukemia were also greater than those of the vehicle controls in animals receiving 150 or 300 mg/kg, although the differences were not statistically significant.

Mononuclear cell leukemia develops spontaneously in F344/N and Wistar Furth rats (Moloney et al., 1969, 1970; Davey and Moloney, 1970). The duration of the disease from onset to death ranges from 2 to 6 weeks (Stromberg and Vogtsberger, 1983). The etiology of this leukemia is not known. The incidences of mononuclear cell leukemia in F344/N and Wistar Furth rats were increased by 3-methylcholanthrene administration and suppressed by X-ray irradiation and splenectomy (Moloney and King, 1971). In the present studies, the incidence of leukemia in the vehicle control male F344/N rats (28%) is greater than the mean incidence observed at this laboratory (17%) or in the overall Program (12%; Appendix F, Table F1). The incidence in the vehicle control female F344/N rats (18%) was somewhat lower than the mean incidence observed at this laboratory (29%) and similar to that in the overall Program (16%; Appendix F, Table F2).

The 600 mg/kg dose of DMMPA significantly increased the incidences of mononuclear cell leukemia in both male (50%) and female (36%) F344/N rats. In most animals, the mononuclear cell leukemia was in an advanced stage (Table 12), with neoplastic cells infiltrating the liver

sinusoids and blood vessels of other organs. The incidence of mononuclear cell leukemia in rats was dose related.

There is convincing evidence that mononuclear cell leukemia was related to the cause of death for many DMMPA-dosed animals dying before the end of the 2-year studies: (1) The majority of these neoplasms were diagnosed as being in an advanced stage; (2) the prevalence of these tumors in animals dying during the last 6 months of the study exceeded (in every dosed and vehicle control group) the corresponding rate observed in older animals killed at the end of the study. Thus, life table analyses are the most appropriate statistical procedure for these neoplasms, and these tests indicate a significant ($P<0.01$) high dose effect for both males and females. The consistency of the effect in both sexes further supports the conclusion that the increased incidence of these tumors was due to administration of DMMPA.

Corn oil appears to be associated with a decreased incidence of mononuclear cell leukemia in male F344/N rats (Haseman et al., 1985). In 36 NTP studies, the incidence of mononuclear cell leukemia in untreated male F344/N rats was 494/1,827 (27% ± 9%). In 23 NTP studies, the incidence of mononuclear cell leukemia in corn oil-gavaged male F344/N rats was 167/1,154 (14% ± 8%). Corn oil did not appear to affect the incidences of mononuclear cell leukemia in female F344/N rats in the NTP studies. The incidence (28%) of mononuclear cell leukemia in the male F344/N vehicle controls in the present study is similar to that in the NTP untreated control male F344/N rats. In the present studies, the rats received corn oil in decreasing doses corresponding to the dose of DMMPA (i.e., the vehicle control rats received 3.3 ml/kg, whereas the high dose rats received 2.5 ml/kg). The somewhat higher dose of corn oil received by the vehicle control rats might have been a factor in suppressing the development of mononuclear cell leukemia in these rats compared with the DMMPA-dosed rats. However, it is unlikely that this slight difference in corn oil dose could explain the increased incidence of mononuclear cell leukemia observed in high dose male rats. Moreover, the hypothesis that corn oil suppresses mononuclear cell leukemia in male F344/N rats requires further study. Finally, female rats (which have shown no evidence of a "corn oil effect") also showed a significant increase in mononuclear cell leukemia at the highest DMMPA dose.

Although there was a positive dose-related trend in the incidence of squamous cell papilloma of the skin in male rats, the increased incidence in the high dose groups was not significant. The locations of the four skin squamous cell papillomas in the high dose male rats were not identical, suggesting that the lesions probably were not related to DMMPA administration.

Mineralization of the renal papilla was observed at increased incidence in the dosed male rats. Rats given DMMPA daily at doses higher than 1.3 g/kg orally for 100 days showed cortical and tubular damage in the kidneys (Coleman, 1977a,b). In the present studies, kidney damage was not observed, probably because the dose of DMMPA was lower. Nevertheless, the incidence of mineral accumulation in the renal papilla observed in the dosed rats may be related to the injurious effects of DMMPA.

Male rats receiving the 600 mg/kg dose of DMMPA had a reduced incidence of pituitary gland adenomas. The cause of this reduction is not clear.

Liver weight was increased in dosed rats in the 13-week studies. Liver enlargement was also observed in the 2-year studies. The enlargement was not accompanied by histopathologic changes, although there was a greater incidence of hepatic angiectasis in the dosed male rats (but not in the dosed female rats). Because the liver is the major site of degradation and detoxification of foreign substances, the liver enlargement observed in the dosed rats may be related to the induction of metabolizing enzymes.

DMMPA did not affect body weight gain of male and female mice or the survival of male mice. The survival of the high dose female mice was marginally lower, due primarily to the death by week 35 of six female mice with lung congestion.

Squamous cell neoplasms of the forestomach are uncommon in corn oil vehicle control male

(7/1,005, 0.7%) and female (4/1,027, 0.4%) $B6C3F_1$ mice in the NTP studies. In the present studies, neoplastic lesions of the forestomach were not found in the vehicle control male and female mice, but squamous cell carcinomas were found in 1/47 low dose female mice and squamous cell papillomas in 2/50 low dose male mice and in 1/46 high dose female mice. In addition, there was also a marginal increase in the incidence of hepatocellular carcinomas in the high dose male mice. The significance of these findings is not clear.

Little information is available in the literature about the metabolism of DMMPA, its reactivity with macromolecules, or its effect on the immune system. DMMPA was not mutagenic in tests with four strains of *Salmonella typhimurium* but was mutagenic in mammalian cells (Appendix L, Tables L1 and L2). It also caused chromosomal aberrations and sister-chromatid exchanges in mammalian cells (Appendix L, Tables L3 and L4). However, DMMPA was mutagenic and clastogenic only at doses over 2 mg/ml and only in the absence of rat or hamster liver S9. The significance of the genetic toxicity of DMMPA to the observed increased incidence of mononuclear cell leukemia is not known.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenicity** for male and female F344/N rats given dimethyl morpholinophosphoramidate, as indicated by increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenicity* for male and female $B6C3F_1$ mice given dimethyl morpholinophosphoramidate at doses of 150 (male), 300, or 600 (female) mg/kg for 2 years.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

1. Arbuzov, B., et al. (1964) Izv. Akad. Nauk. SSSR., Ser. Khim. 4:661- 669. (C.A. 3099a, Vol. 61, 1964).

2. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

3. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

4. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S.; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications (in press).

5. Clive, D.; Johnson, K.; Spector, J.; Batson, A.; Brown, M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

6. Coleman, I. (1977a) Toxicity of DMMPA, Part I. The Acute Effects of DMMPA. Technical Paper No. 466. Suffield, Canada: Defence Research Establishment.

7. Coleman, I. (1977b) Toxicology of DMMPA, Part II. The Effects of Chronic Application of DMMPA to Test Animals. Technical Paper No. 467. Suffield, Canada: Defence Research Establishment.

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

9. Davey, F.; Maloney, W. (1970) Postmortem observations on Fischer rats with leukemia and other disorders. Lab. Invest. 23:327-334.

10. Dawson, R.; Lakeland, B.; Poretski, M.; Bladen, M. (1978) Dimethylmorpholinophosphoramidate (DMMPA) Persistence in Various Tissues of the Rat. Department of Defense Material Research Laboratory Report (Australia), MRL-R-705.

11. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974.

12. Goto, K.; Maeda, S.; Kano, Y.; Sugimura, T. (1978) Factors involved in differential Giemsa-staining of sister chromatids. Chromosoma 66:351-359.

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

14. Haseman J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

15. Haseman, J.; Huff, J.; Boorman, G.; Rao, G.; Arnold, J.; McConnell, E. (1985) Neoplasms observed in untreated corn oil gavage control groups of F344/N rats and B6C3F$_1$ mice. J. Natl. Cancer Inst. (in press).

16. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3-142.

17. Jones, H., Jr.; Meyer, B.; Karel, L. (1948) The relationship of cholinesterase inhibiting activity to the toxicity of some organic phosphorus compounds. Med. Div. Report No. 134. Department of the Army, Chemical Corps.

18. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

19. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

20. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

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

22. McNally, W.; Adie, P. (1977) Studies on the Total Intake Simulant DMMPA (U). Technical Paper No. 469. Suffield, Canada: Defence Research Establishment.

23. Miller, R., Jr. (1981) Simultaneous Statistical Inference, 2nd ed. New York: Springer-Verlag, Inc., pp. 76-81.

24. Moloney, W.; King, V. (1971) Reduction of leukemia incidence following splenectomy in the rat. Cancer Res. 33:573-574.

25. Moloney, W.; Boschetti, A.; King, V. (1969) Observations on leukemia in Wistar Furth rats. Cancer Res. 29:938-946.

26. Moloney, W.; Boschetti, A.; King, V. (1970) Spontaneous leukemia in Fischer rats. Cancer Res. 30:41-43.

27. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1, February.

28. National Institutes of Health (NIH) (1978) NIH Specification NIH- 11-133f, November 1.

29. National Toxicology Program (NTP) (1984) Toxicology and Carcinogenesis Studies of Tris(2-ethylhexyl)phosphate in F344/N Rats and B6C3F_1 Mice. NTP TR 274. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

30. National Toxicology Program (NTP) (1985) Toxicology and Carcinogenesis Studies of Dimethyl Hydrogen Phosphite in F344/N Rats and B6C3F_1 Mice. NTP TR 287. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

31. Perry, P.; Wolff, S. (1974) New Giemsa method for differential staining of sister chromatids. Nature (London) 251:156-158.

32. San, R. (1984) Biological Testing of H1-6 and DMMPA for Genotoxic Activity in Mammalian Cell Cultures. CR-25-84. Defence Research Establishment, Suffield, Ralston, Alberta, Canada.

33. Stromberg, P.; Vogtsberger, L. (1983) Pathology of the mononuclear cell leukemia of Fischer rats. I. Morphologic studies. Vet. Pathol. 20:698-708.

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

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	1 (2%)	4 (8%)
BASAL-CELL TUMOR	1 (2%)			
TRICHOEPITHELIOMA			1 (2%)	
ADNEXAL ADENOMA		2 (4%)	1 (2%)	
KERATOACANTHOMA		1 (2%)	2 (4%)	
FIBROMA		3 (6%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FIBROMA	3 (6%)	3 (6%)	4 (8%)	1 (2%)
FIBROSARCOMA		1 (2%)		
LIPOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, MET				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)		1 (2%)
FIBROSARCOMA, METASTATIC		1 (2%)		
OSTEOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS				1 (2%)
LEUKEMIA, MONONUCLEAR CELL	14 (28%)	21 (42%)	19 (38%)	25 (50%)
#MEDIASTINAL L. NODE	(50)	(49)	(50)	(48)
TRANSITIONAL-CELL CARCINOMA, MET				1 (2%)
CIRCULATORY SYSTEM				
#SPLEEN	(50)	(50)	(50)	(50)
HEMANGIOMA		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	3 (6%)	3 (6%)	3 (6%)
#PANCREAS	(50)	(49)	(47)	(47)
TRANSITIONAL-CELL CARCINOMA, INV				1 (2%)
ACINAR-CELL ADENOMA			2 (4%)	
#JEJUNUM	(50)	(50)	(47)	(46)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
#URINARY BLADDER	(49)	(50)	(49)	(50)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY INTERMEDIA	(50)	(50)	(48)	(50)
ADENOMA, NOS			1 (2%)	
#ANTERIOR PITUITARY	(50)	(50)	(48)	(50)
ADENOMA, NOS	7 (14%)	4 (8%)	7 (15%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#ADRENAL	(49)	(50)	(50)	(50)
PHEOCHROMOCYTOMA	9 (18%)	16 (32%)	10 (20%)	5 (10%)
#THYROID	(50)	(48)	(48)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)		2 (4%)	1 (2%)
FOLLICULAR-CELL CARCINOMA			2 (4%)	
C-CELL ADENOMA	4 (8%)	3 (6%)	4 (8%)	2 (4%)
C-CELL CARCINOMA		2 (4%)		
#PARATHYROID	(43)	(40)	(38)	(45)
ADENOMA, NOS				1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(47)	(47)
ISLET-CELL ADENOMA	4 (8%)		2 (4%)	
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)	
FIBROADENOMA	3 (6%)	4 (8%)	1 (2%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)			1 (2%)
ADENOMA, NOS	1 (2%)	1 (2%)	3 (6%)	2 (4%)
#PROSTATE	(48)	(45)	(49)	(48)
ADENOMA, NOS				1 (2%)
#TESTIS	(50)	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	45 (90%)	45 (90%)	44 (88%)	46 (94%)
MESOTHELIOMA, NOS			1 (2%)	
MESOTHELIOMA, MALIGNANT			2 (4%)	
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)			
#CEREBELLUM	(50)	(50)	(50)	(50)
GRANULAR-CELL TUMOR, NOS		1 (2%)		
SPECIAL SENSE ORGANS				
*ZYMBAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		1 (2%)	
MUSCULOSKELETAL SYSTEM				
*KNEE JOINT	(50)	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)			
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, INV				1 (2%)
MESOTHELIOMA, NOS			1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	1 (2%)	
MESOTHELIOMA, INVASIVE			2 (4%)	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	3	6	9	22
MORIBUND SACRIFICE	10	7	13	5
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	37	37	28	22
DOSING ACCIDENT				
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS				1
ANIMAL MISSING				
ANIMAL MISSEXED				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	49	47	48	49
TOTAL PRIMARY TUMORS	102	117	119	98
TOTAL ANIMALS WITH BENIGN TUMORS	48	46	48	47
TOTAL BENIGN TUMORS	81	88	88	66
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	24	22	28
TOTAL MALIGNANT TUMORS	19	24	25	29
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	1	2	1
TOTAL SECONDARY TUMORS	1	1	2	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	5	6	3
TOTAL UNCERTAIN TUMORS	2	5	6	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(49)	(50)
ADNEXAL ADENOMA	1 (2%)			
FIBROMA	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(49)	(50)
FIBROMA	1 (2%)	1 (2%)	1 (2%)	
FIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(49)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)		
CORTICAL CARCINOMA, METASTATIC		1 (2%)		
OSTEOSARCOMA, INVASIVE		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
LEUKEMIA, MONONUCLEAR CELL	9 (18%)	13 (26%)	12 (24%)	18 (36%)
#SPLEEN	(50)	(50)	(49)	(49)
ACINAR-CELL CARCINOMA, INVASIVE		1 (2%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(49)	(50)
NEOPLASTIC NODULE			1 (2%)	
HEPATOCELLULAR CARCINOMA				1 (2%)
ACINAR-CELL CARCINOMA, MET		1 (2%)		
#PANCREAS	(50)	(49)	(48)	(49)
ACINAR-CELL CARCINOMA		1 (2%)		
#COLON	(50)	(48)	(48)	(49)
LEIOMYOSARCOMA		1 (2%)		
URINARY SYSTEM				
#URINARY BLADDER	(49)	(48)	(48)	(50)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)			
ENDOCRINE SYSTEM				
#ANTERIOR PITUITARY	(50)	(50)	(46)	(50)
CARCINOMA, NOS	2 (4%)	2 (4%)		
ADENOMA, NOS	9 (18%)	14 (28%)	14 (30%)	13 (26%)
#ADRENAL	(50)	(50)	(49)	(50)
CORTICAL ADENOMA				1 (2%)
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA	1 (2%)	5 (10%)	3 (6%)	2 (4%)
GANGLIONEUROMA	1 (2%)			
GANGLIONEUROBLASTOMA			1 (2%)	
#THYROID	(50)	(50)	(49)	(48)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)	
C-CELL ADENOMA	2 (4%)		1 (2%)	1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#PANCREATIC ISLETS	(50)	(49)	(48)	(49)
ISLET-CELL ADENOMA	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(49)	(50)
ADENOMA, NOS		1 (2%)		1 (2%)
ADENOCARCINOMA, NOS		1 (2%)		
CYSTADENOMA, NOS	1 (2%)		1 (2%)	
INTRADUCTAL PAPILLOMA		1 (2%)	1 (2%)	
FIBROADENOMA	11 (22%)	11 (22%)	12 (24%)	3 (6%)
*CLITORAL GLAND	(50)	(50)	(49)	(50)
CARCINOMA, NOS		1 (2%)		2 (4%)
ADENOMA, NOS	2 (4%)	1 (2%)	1 (2%)	
#UTERUS	(50)	(50)	(49)	(50)
ADENOCARCINOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP	6 (12%)	5 (10%)	10 (20%)	7 (14%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)			
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)	(50)
ADENOMA, NOS		2 (4%)		
ADENOCARCINOMA, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN STEM	(50)	(50)	(49)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)		
SPECIAL SENSE ORGANS				
*ZYMBAL GLAND	(50)	(50)	(49)	(50)
CARCINOMA, NOS		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*STERNUM	(50)	(50)	(49)	(50)
GANGLIONEUROBLASTOMA, MET			1 (2%)	
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(49)	(50)
OSTEOSARCOMA		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
ADENOCARCINOMA, NOS, INVASIVE			1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET	1 (2%)			
DIAPHRAGM				
GANGLIONEUROBLASTOMA, MET			1	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	6	8	3	13
MORIBUND SACRIFICE	8	7	10	13
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	36	35	33	24
DOSING ACCIDENT			2	
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS			1	
ANIMAL MISSING				
ANIMAL MISSEXED			1	
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	35	37	35	34
TOTAL PRIMARY TUMORS	52	66	60	50
TOTAL ANIMALS WITH BENIGN TUMORS	29	27	29	21
TOTAL BENIGN TUMORS	39	43	45	28
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	21	14	21
TOTAL MALIGNANT TUMORS	13	23	14	22
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	4	2	
TOTAL SECONDARY TUMORS	1	5	4	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	105	105	096	105	105	105	077	105	105	105	105	105	096	105	105	105	071	105	105	105	091	105	078	091
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	−	−	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X							X			X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Pheochromocytoma		X	X									X			X			X		X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									X
C-cell adenoma																X				X					
Parathyroid	+	+	+	−	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma	X								X																
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+
Fibroadenoma											X														
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral 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
Carcinoma, NOS																									
Adenoma, NOS												X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma				X																					
SPECIAL SENSE ORGANS																									
Zymbal 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
Carcinoma, NOS																								X	
MUSCULOSKELETAL SYSTEM																									
Joint	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
Osteosarcoma																									
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
Mesothelioma, NOS																									
Leukemia, mononuclear cell				X														X				X			X

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: 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 RATS: VEHICLE CONTROL (Continued)

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	105	105	105	105	105	080	098	105	105	105	105	105	105	098	105	085	105	105	105	105	105	082	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma			X																							1
Basal cell tumor												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																	X					X				3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
Osteosarcoma, metastatic								X																		1
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS						X					X					X			X							7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																		X					X		X	9
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																									X	2
C-cell adenoma																X	X									4
Parathyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																		X	X							4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	*50
Fibroadenoma										X					X											3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral 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
Carcinoma, NOS													X												X	2
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal 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
Carcinoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Joint	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
Osteosarcoma								X																		1
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
Mesothelioma, NOS																X										1
Leukemia, mononuclear cell				X	X		X		X	X				X				X	X			X	X			14

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	088	105	105	105	105	095	105	078	065	105	060	105	105	100	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Adnexal adenoma																									
Keratoacanthoma																					X				
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X				X						
Fibrosarcoma																									
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Fibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X																					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X		X		X						X	X		X			X		X	X	X	X		
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X																	X				
C-cell carcinoma																						X			
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	–	+	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibroadenoma						X					X			X											
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral 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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, 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
Mesothelioma, NOS														X											
Leukemia, mononuclear cell	X				X	X				X						X			X		X		X	X	

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

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	105	105	105	089	105	105	105	105	088	105	104	105	225	105	105	105	105	105	091	105	105	105	087	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Adnexal adenoma																			X			X				2
Keratoacanthoma																										1
Fibroma				X	X						X															3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X																								3
Fibrosarcoma																			X							1
Lipoma												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				2
Fibrosarcoma, metastatic																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma					X																					1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule												X			X											3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X																					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS						X								X												4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X	X			X						X									X						16
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma																								X		3
C-cell carcinoma																				X						2
Parathyroid	+	+	+	–	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroadenoma															X											4
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	45
Prostate	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	45
Preputial/clitoral 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												1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
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
Mesothelioma, NOS																										1
Leukemia, mononuclear cell			X	X	X	X	X			X		X			X	X	X				X		X			21

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: MID DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	1 0 5	0 9 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 8 9	0 7 3	0 9 2	1 0 4	0 8 5	0 9 0	1 0 5	1 0 5	0 9 2	0 6 0	1 0 5	1 0 5	0 9 1	0 9 3	1 0 5	0 8 5	1 0 5
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Trichoepithelioma																									
Adnexal adenoma																									
Keratoacanthoma		X																							
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X																		X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+
Acinar cell adenoma																									X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma										X															
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS				X						X						X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X											X						X		
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma							X																		X
C-cell adenoma					X														X						
Parathyroid	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Islet cell adenoma														X		X									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
Mesothelioma, NOS																									
Mesothelioma, malignant																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral 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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal 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
Carcinoma, NOS																									
BODY CAVITIES																									
Peritoneum	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
Mesothelioma, 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
Mesothelioma, NOS																									X
Mesothelioma, invasive																									
Leukemia, mononuclear cell	X		X					X			X	X		X							X	X	X		X

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

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	105	093	105	105	105	104	105	097	089	105	102	105	105	064	105	105	078	105	105	105	105	105	095	104	096	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma	X																									1
Trichoepithelioma													X													1
Adnexal adenoma																				X						1
Keratoacanthoma	X																									2
Fibroma																X										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma										X												X		X		4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																			X							3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Acinar cell adenoma										X																2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS										X	X								X				X		X	8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X		X				X							X				X	X	X				10
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Follicular cell adenoma												X			X											2
Follicular cell carcinoma																										2
C-cell adenoma																		X					X			4
Parathyroid	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma																										2
Islet cell carcinoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	N	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenoma, NOS																							X			1
Fibroadenoma										X																1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	44
Mesothelioma, NOS																	X									1
Mesothelioma, malignant								X																	X	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral 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	X			3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal 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
Carcinoma, NOS																	X									1
BODY CAVITIES																										
Peritoneum	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
Mesothelioma, NOS																										1
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
Mesothelioma, NOS																										1
Mesothelioma, invasive								X																	X	2
Leukemia, mononuclear cell	X	X				X		X	X	X		X					X							X		19

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: *HIGH DOSE*

ANIMAL NUMBER	00101	00102	00103	00104	00105	00106	00107	00108	00109	00110	00111	00112	00113	00114	00115	00116	00117	00118	00119	00120	00121	00122	00123	00124	00125
WEEKS ON STUDY	09 1	10 3	10 5	10 5	08 7	10 5	06 6	10 5	10 5	08 5	09 8	10 5	10 5	10 5	10 5	10 5	09 6	10 4	10 5	10 4	09 5	10 5	07 0	10 5	10 2
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X												X										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma, metastatic																									
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X			X																					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma, invasive																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X							X										
Thyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma		X												X											
Parathyroid	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X																	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+
Fibroadenoma																			X						
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Preputial/clitoral 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
Carcinoma, NOS																									
Adenoma, NOS												X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	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
Transitional cell carcinoma, invasive																									
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																									
Leukemia, mononuclear cell	X	X						X			X	X					X	X	X		X	X			X

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

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	105	086	105	083	080	095	105	105	038	099	105	105	100	094	105	105	060	105	103	103	086	092	103	093	105	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma				X							X															4
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma, metastatic										X																1
Alveolar/bronchiolar adenoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell carcinoma, metastatic										X																1
Thymus	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	–	–	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																					X					3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	47
Transitional cell carcinoma, invasive										X																1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	46
Adenocarcinoma, NOS																						X				1
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X				X												X								5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																				X						1
C-cell adenoma																										2
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	45
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroadenoma												X														2
Testis	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X		X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	46
Prostate	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Adenoma, NOS																										1
Preputial/clitoral 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
Carcinoma, NOS															X											1
Adenoma, NOS																			X							2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	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
Transitional cell carcinoma, invasive										X																1
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																				1
Leukemia, mononuclear cell		X		X	X		X	X			X		X	X	X	X	X	X	X					X		25

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	105	104	105	105	105	105	105	105	085	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adnexal adenoma																	X								
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																				X					
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																						X			
Adenoma, NOS				X				X																X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Ganglioneuroma									X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma							X																		
Parathyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Cystadenoma, NOS								X																	
Fibroadenoma							X	X							X						X	X		X	
Preputial/clitoral 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																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X								X															X	
Endometrial stromal sarcoma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Endometrial stromal sarcoma, metastatic																									
Leukemia, mononuclear cell	X								X	X															

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: 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 RATS: VEHICLE CONTROL (Continued)

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	105	105	105	105	076	105	084	105	062	105	105	105	096	103	094	083	101	105	105	081	102	105	105	099	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adnexal adenoma																										1
Fibroma																X										1
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS													X													2
Adenoma, NOS	X									X	X			X							X				X	9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma														X												1
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma		X																								2
Parathyroid	+	−	+	+	+	+	+	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma				X																						1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Cystadenoma, NOS																										1
Fibroadenoma	X					X	X												X			X				11
Preputial/clitoral 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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp		X	X										X													6
Endometrial stromal sarcoma									X																	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Endometrial stromal sarcoma, metastati									X																	1
Leukemia, mononuclear cell			X		X											X	X		X						X	9

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	105	105	087	105	092	097	105	105	105	105	105	065	105	105	105	105	105	105	064	105	099	105	087	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Cortical carcinoma, metastatic																	X								
Osteosarcoma, invasive																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma, invasive																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma			X																						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS						X			X		X		X			X		X				X	X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																	X								
Pheochromocytoma								X															X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
Parathyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Intraductal papilloma																									
Fibroadenoma		X					X		X						X			X				X			
Preputial/clitoral 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
Carcinoma, NOS																						X			
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp															X			X					X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Zymbal 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
Carcinoma, NOS																									
BODY CAVITIES																									
Mediastinum	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
Osteosarcoma																									
ALL OTHERS																									
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
Leukemia, mononuclear cell							X			X	X										X		X		

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

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	099	105	105	068	105	105	105	105	105	105	105	105	099	105	095	105	092	031	105	105	105	064	079	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma										X																1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Cortical carcinoma, metastatic																										1
Osteosarcoma, invasive																		X								1
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell carcinoma, invasive																								X		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	−	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell carcinoma, metastatic																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell carcinoma																								X		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Leiomyosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS						X														X						2
Adenoma, NOS			X				X							X					X						X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma																										1
Pheochromocytoma																		X			X				X	5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	43
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenoma, NOS																				X						1
Adenocarcinoma, NOS												X														1
Intraductal papilloma						X																				1
Fibroadenoma			X			X								X						X			X			11
Preputial/clitoral 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
Carcinoma, NOS																										1
Adenoma, NOS																								X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS							X	X																		2
Endometrial stromal polyp											X								X							5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive						X																				1
SPECIAL SENSE ORGANS																										
Zymbal 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
Carcinoma, NOS	X																									1
BODY CAVITIES																										
Mediastinum	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
Osteosarcoma																		X								1
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
Leukemia, mononuclear cell							X	X				X		X		X				X	X			X		13

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: MID 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	105	105	105	105	105	097	105	053	071	102	105	093	105	102	102	087	105	096	105	105	105	095	096	105	038
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																						X			
Trachea	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X			X	X		X		X	X				X					X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma												X													
Ganglioneuroblastoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma					X																				
C-cell adenoma																									
Parathyroid	–	–	–	+	–	+	+	+	+	–	+	+	+	–	+	–	–	+	+	+	–	–	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS			X																						
Intraductal papilloma												X													
Fibroadenoma		X	X		X		X					X						X	X						
Preputial/clitoral 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																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Endometrial stromal polyp															X			X		X			X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	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
Ganglioneuroblastoma, metastatic																									
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
Adenocarcinoma, NOS, invasive																						X			
Leukemia, mononuclear cell						X			X	X					X			X					X		
Diaphragm NOS																									
Ganglioneuroblastoma, metastatic																									

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID DOSE (Continued)

ANIMAL NUMBER	023	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	105	105	105	001	105	105	105	105	105	105	105	069	102	105	102	105	105	105	105	105	105	105	105	033	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue																										49
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Trachea	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule	X																									1
Bile duct	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
Pancreas	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	S	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS							X		X				X				X			X						14
Adrenal	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma								X															X			3
Ganglioneuroblastoma															X											1
Thyroid	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
C-cell adenoma										X																1
Parathyroid	+	+	+	S	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	−	+	+	+	−	+	33
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, NOS																										1
Intraductal papilloma																										1
Fibroadenoma		X	X										X						X		X					12
Preputial/clitoral gland	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
Adenoma, NOS					X																					1
Uterus	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Endometrial stromal polyp							X		X				X					X	X		X					10
Ovary	+	+	+	S	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
Ganglioneuroblastoma, metastatic															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
Adenocarcinoma, NOS, invasive																										1
Leukemia, mononuclear cell							X	X	X										X		X			X		12
Diaphragm NOS				S																						1
Ganglioneuroblastoma, metastatic															X											1

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	103	105	083	105	105	098	105	105	105	105	105	105	105	083	105	105	105	080	105	105	105	103	035	091	105
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS			X				X	X	X							X		X						X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cortical adenoma																					X				
Pheochromocytoma	X																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
C-cell adenoma																						X			
Parathyroid	+	+	+	+	+	−	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	−	−	+	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	
Adenoma, NOS							X																		
Fibroadenoma																			X						
Preputial/clitoral 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	
Carcinoma, NOS					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, NOS												X													
Endometrial stromal polyp														X							X	X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
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	
Leukemia, mononuclear cell	X					X			X					X					X			X		X	X

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

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	093	105	079	063	100	040	105	083	096	064	095	105	105	034	088	105	036	098	036	105	097	105	105	080	098	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+		48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymus	+	−	+	+	−	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+		44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma										X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−		49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma, NOS	X						X				X	X							X			X				13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cortical adenoma																										1
Pheochromocytoma																						X				2
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
C-cell adenoma																										1
Parathyroid	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Adenoma, NOS																										1
Fibroadenoma									X													X				3
Preputial/clitoral 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
Carcinoma, NOS				X																						2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenocarcinoma, NOS																										1
Endometrial stromal polyp								X														X	X	X		7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
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		*50
Leukemia, mononuclear cell	X	X			X						X	X			X	X		X		X					X	18

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	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)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	2 (4%)	2 (4%)	1 (2%)
FIBROMA		1 (2%)	
FIBROSARCOMA	3 (6%)	1 (2%)	1 (2%)
MYXOSARCOMA		1 (2%)	
LIPOMA			1 (2%)
NEUROFIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	6 (12%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG. LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		1 (2%)
#LUNG	(50)	(50)	(50)
KUPFFER-CELL SARCOMA, METASTATIC			1 (2%)
#LIVER	(50)	(50)	(50)
KUPFFER-CELL SARCOMA	1 (2%)		1 (2%)
#THYMUS	(41)	(40)	(46)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(50)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA		1 (2%)	2 (4%)
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		2 (4%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
ISLET-CELL CARCINOMA, METASTATIC			1 (2%)
BILE DUCT CARCINOMA		1 (2%)	
HEPATOCELLULAR ADENOMA	6 (12%)	8 (16%)	4 (8%)
HEPATOCELLULAR CARCINOMA	6 (12%)	6 (12%)	12 (24%)
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		2 (4%)	
URINARY SYSTEM			
NONE			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(48)	(47)	(48)
ADENOMA, NOS	1 (2%)	1 (2%)	
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	2 (4%)		
#ADRENAL/CAPSULE	(50)	(50)	(50)
ADENOMA, NOS		2 (4%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID	(49)	(50)	(47)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
PAPILLARY ADENOMA			2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC		1 (2%)	
SARCOMA, NOS, METASTATIC		1 (2%)	
FIBROSARCOMA, INVASIVE	1 (2%)		
MYXOSARCOMA, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	3	8	7
MORIBUND SACRIFICE	6	7	4
TERMINAL SACRIFICE	41	35	39

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	26	29	25
TOTAL PRIMARY TUMORS	32	47	35
TOTAL ANIMALS WITH BENIGN TUMORS	14	20	12
TOTAL BENIGN TUMORS	15	23	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	20	18
TOTAL MALIGNANT TUMORS	17	24	21
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	4	4
TOTAL SECONDARY TUMORS	2	4	4

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		3	
ANIMALS NECROPSIED	50	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	47	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(47)	(50)
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(47)	(50)
SARCOMA, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(46)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	2 (4%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(50)
MALIGNANT LYMPHOMA, NOS	6 (12%)	6 (13%)	5 (10%)
MALIG. LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
GRANULOCYTIC LEUKEMIA		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(32)	(34)	(38)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
CIRCULATORY SYSTEM			
*ADIPOSE TISSUE	(50)	(47)	(50)
HEMANGIOMA	1 (2%)		
#UTERUS	(50)	(47)	(49)
HEMANGIOMA	1 (2%)		1 (2%)
#OVARY	(49)	(45)	(48)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(47)	(49)
HEPATOCELLULAR ADENOMA	4 (8%)	2 (4%)	
HEPATOCELLULAR CARCINOMA	3 (6%)	2 (4%)	2 (4%)
#STOMACH	(50)	(47)	(46)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#FORESTOMACH	(50)	(47)	(46)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#DUODENUM	(50)	(44)	(45)
ADENOMATOUS POLYP, NOS	1 (2%)		
#JEJUNUM	(50)	(44)	(45)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(46)	(41)
CHROMOPHOBE ADENOMA	10 (20%)	7 (15%)	6 (15%)
#ADRENAL	(50)	(47)	(50)
PHEOCHROMOCYTOMA		2 (4%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#THYROID	(45)	(47)	(45)
FOLLICULAR-CELL ADENOMA	2 (4%)		1 (2%)
CYSTADENOMA, NOS	1 (2%)		
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(47)	(50)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
#UTERUS	(50)	(47)	(49)
ADENOMA, NOS		1 (2%)	
LEIOMYOMA		1 (2%)	
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	1 (2%)	2 (4%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
#OVARY	(49)	(45)	(48)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(47)	(50)
PAPILLARY ADENOCARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF NECK	(50)	(47)	(50)
SARCOMA, NOS			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(50)
SARCOMA, NOS, METASTATIC			1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	5	11
MORIBUND SACRIFICE	4	3	5
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	41	39	34
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1		
ANIMAL MISSING		3	
ANIMAL MISSEXED			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	31	28	24
TOTAL PRIMARY TUMORS	42	32	29
TOTAL ANIMALS WITH BENIGN TUMORS	23	15	12
TOTAL BENIGN TUMORS	26	18	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	14	14
TOTAL MALIGNANT TUMORS	16	14	16
TOTAL ANIMALS WITH SECONDARY TUMORS##			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: VEHICLE CONTROL

ANIMAL NUMBER	00001	00002	00003	00004	00005	00006	00007	00008	00009	00010	00011	00012	00013	00014	00015	00016	00017	00018	00019	00020	00021	00022	00023	00024	00025
WEEKS ON STUDY	10505	10505	09303	10405	10505	10405	10705	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	10505	08809	10305	08101	10205
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS	X																							X	
Fibrosarcoma																	X		X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																						X			
Alveolar/bronchiolar adenoma			X				X		X																
Alveolar/bronchiolar carcinoma						X																			
Trachea	−	−	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					X				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+
Thymus	+	+	−	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X				X	X	X				X						
Hepatocellular carcinoma														X						X		X			
Kupffer cell sarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X																					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma										X															
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Fibrosarcoma, invasive																									
Malignant lymphoma, histiocytic type				X																					
Malignant lymphoma, mixed type			X																						

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

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	105	089	105	105	105	105	098	105	105	105	105	105	105	105	105	105	105	086	045	072	105	105	105	105	086	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibrosarcoma											X															3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma									X															X		5
Alveolar/bronchiolar carcinoma									X																	2
Trachea	−	+	+	+	−	+	+	+	−	+	+	−	−	−	−	−	−	+	−	+	−	−	−	−	−	27
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Lymph nodes	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Thymus	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					6
Hepatocellular carcinoma		X					X																	X		6
Kupffer cell sarcoma															X											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	48
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma				X																						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Parathyroid	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	+	+	+	−	+	+	−	37
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Fibrosarcoma, invasive											X															1
Malignant lymphoma, histiocytic type																									X	2
Malignant lymphoma, mixed type																										1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	094	032	093	105	105	105	104	096	105	105	105	105	099	105	105	105	099	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Fibroma																									
Subcutaneous tissue																									
Sarcoma, NOS																									
Fibroma																									
Fibrosarcoma																									
Myxosarcoma																									
Neurofibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X												
Alveolar/bronchiolar adenoma				X	X		X	X				X												X	
Alveolar/bronchiolar carcinoma												X								X					
Trachea	−	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Lymph nodes	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	−	−	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma																									
Hepatocellular adenoma												X					X				X				
Hepatocellular carcinoma													X												
Hemangiosarcoma									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																								X	
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Bile duct carcinoma, metastatic																									
Sarcoma, NOS, metastatic																						X			
Myxosarcoma, metastatic																									
Malignant lymphoma, NOS													X												
Malignant lymphoma, undiffer type							X																		
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type																	X								

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

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	105	105	105	105	105	105	105	105	105	105	086	105	096	105	092	083	080	105	105	105	105	105	105	095	089	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma													X													1
Fibroma																									X	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibroma							X																			1
Fibrosarcoma																								X		1
Myxosarcoma													X													1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																										6
Alveolar/bronchiolar carcinoma															X											3
Trachea	+	+	–	–	–	+	+	–	–	–	+	–	–	–	+	–	+	+	+	+	–	–	+	+	+	30
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	–	40
Malignant lymphoma, lymphocytic type										X																1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma																X										1
Hepatocellular adenoma							X			X	X			X									X			8
Hepatocellular carcinoma															X	X							X		X	X	6
Hemangiosarcoma										X																2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																			X					2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS							X																			1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X																		2
Pheochromocytoma																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
Parathyroid	+	+	–	–	–	–	–	–	–	–	+	–	–	–	+	+	+	+	+	–	–	–	+	–	–	23
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Bile duct carcinoma, metastatic																										
Sarcoma, NOS, metastatic																										
Myxosarcoma, metastatic																										
Malignant lymphoma, NOS																										
Malignant lymphoma, undiffer type																										
Malignant lymphoma, lymphocytic type																										
Malignant lymphoma, histiocytic type																										

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	059	105	105	105	105	105	105	090	105	099	105	105	105	103	105	105	093	105	105	105	105	105	105	031	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma																	X								
Lipoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																X									
Alveolar/bronchiolar adenoma											X	X													
Alveolar/bronchiolar carcinoma																X									
Kupffer cell sarcoma, metastatic													X												
Trachea	–	–	–	–	+	+	+	+	+	+	–	+	–	+	+	–	+	–	+	+	+	–	+	+	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X							X								
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma, metastatic																									
Hepatocellular adenoma								X			X														
Hepatocellular carcinoma	X										X			X	X	X	X								
Hemangiosarcoma, metastatic										X															
Kupffer cell sarcoma													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	–	+	+	+	–	–	–	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
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
Papillary adenoma																									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
Malignant lymphoma, NOS								X																	
Malignant lymphoma, mixed type																		X							

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0268	0271	0289	0290	0301	0312	0333	0334	0335	0336	0337	0338	0339	0401	0411	0422	0433	0444	0455	0466	0477	0488	0499	0501	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	004	105	105	105	004	105	105	005	105	099	105	105	105	105	105	101	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																			X						1
Fibrosarcoma																									1
Lipoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																									1
Alveolar/bronchiolar adenoma		X			X												X				X				6
Alveolar/bronchiolar carcinoma																									1
Kupffer cell sarcoma, metastatic																									1
Trachea	−	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	+	+	−	−	+	+	+	+	−	28
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma, metastatic								X																		1
Hepatocellular adenoma		X																	X							4
Hepatocellular carcinoma			X	X						X				X				X						X		12
Hemangiosarcoma, metastatic																										1
Kupffer cell sarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma							X																			1
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	−	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	+	−	−	−	−	+	−	+	−	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma								X																		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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*50
Papillary adenoma											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	*50
Malignant lymphoma, NOS																									1
Malignant lymphoma, mixed type																									1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	105	092	105	105	105	105	105	105	105	105	105	105	080	105	105	105	105	105	105	105	105	101	096	105	105
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X					X	
Alveolar/bronchiolar carcinoma													X										X		
Trachea	+	+	+	+	−	+	+	+	−	−	+	−	−	−	−	+	+	+	−	+	−	−	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	−	+	−	+	−	+	+	+	−
Thymus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X								
Hepatocellular carcinoma				X				X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																							X		
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma										X				X	X					X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Follicular cell adenoma																		X							
Cystadenoma, NOS																									
Papillary cystadenoma, NOS																									
Parathyroid	−	+	−	−	−	−	+	−	−	+	+	−	+	−	−	−	−	+	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																									
Hemangioma							X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
Hemangioma																				X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		X													X			
Malignant lymphoma, undiffer type																									
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									
Adipose tissue																									
Hemangioma				X																					

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

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	105	105	105	105	105	052	105	105	105	105	105	105	084	103	105	105	105	105	105	105	105	092	105	073	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																										2
Trachea	−	−	+	+	+	−	−	+	−	+	+	−	+	+	+	−	−	−	+	−	−	+	−	−	−	25
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	−	−	+	−	−	−	+	−	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	32
Thymus	+	+	+	+	−	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X	X						X																4
Hepatocellular carcinoma								X																		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+		48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma	X	X					X							X					X							10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	45
Follicular cell adenoma		X																								2
Cystadenoma, NOS																					X					1
Papillary cystadenoma, NOS						X																				1
Parathyroid	−	+	−	−	+	−	−	+	−	+	+	−	+	+	+	−	−	−	+	−	−	+	+	+	−	24
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma										X																1
Endometrial stromal polyp									X																	1
Hemangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS					X																					1
Hemangioma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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				6
Malignant lymphoma, undiffer type																								X		1
Malignant lymphoma, histiocytic type										X																1
Malignant lymphoma, mixed type	X																									1
Adipose tissue																										
Hemangioma																										1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: 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	105	105	105	105	105	105	105	065	105	084	105	105	105	100	105	105	065	105	105	105	105	105	105	099	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	−	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	−	−	+	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	−	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−
Malignant lymphoma, NOS																									
	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X																	X							
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma								X																	
Small intestine	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma												X		X				X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																						X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	+	+	−	−	−	+	+	−	+	−	+	−	+	+	−	−	−	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X												
Leiomyoma												X													
Endometrial stromal polyp						X	X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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								X													X	X	
Malignant lymphoma, histiocytic type																	X								
Granulocytic leukemia								X																	

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

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	105	105	105	105	105	001	001	105	001	105	105	105	105	105	105	105	092	105	096	105	105	105	105	075	105	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*47
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar adenoma										X					X											2
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	−	M	M	−	M	+	+	−	+	+	+	−	−	−	+	−	−	−	−	−	−	28
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	−	−	+	+	+	M	M	+	M	+	−	+	+	−	+	+	+	+	+	+	+	−	−	+	+	34
Malignant lymphoma, NOS			X																							1
Thymus	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	−	−	+	−	+	+	+	+	−	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma																										2
Hepatocellular carcinoma																			X	X						2
Bile duct	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	N	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*47
Pancreas	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	−	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma																										1
Small intestine	+	+	−	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Chromophobe adenoma	X			X				X															X			7
Adrenal	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma	X																									2
Thyroid	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	−	−	+	+	−	M	M	+	M	+	−	+	+	+	+	−	−	+	+	−	+	−	+	−	−	26
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	M	M	+	M	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*47
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS																										1
Leiomyoma																										1
Endometrial stromal polyp																										2
Ovary	+	+	+	+	+	M	M	+	M	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	M	M	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*47
Malignant lymphoma, NOS															X									X		6
Malignant lymphoma, histiocytic type																										1
Granulocytic leukemia																										1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE: *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	105	105	105	025	105	100	105	009	058	105	086	035	105	105	105	019	105	105	105	105	105	023	023	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X										X										
Alveolar/bronchiolar carcinoma			X																						
Trachea	−	−	+	−	−	+	−	−	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	−	+	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X																						
Bile duct	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma	X																								
Large intestine	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	−
Chromophobe adenoma		X								X							X	X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	+	+	+	+	−	−	−	+	−	−	−	−	−	−	+	+	+	+	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Uterus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Endometrial stromal sarcoma											X														
Hemangioma																									
Ovary	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Papillary adenocarcinoma															X										
MUSCULOSKELETAL SYSTEM																									
Muscle	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
Sarcoma, 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
Sarcoma, NOS, metastatic																									
Malignant lymphoma, NOS																									
Malignant lymphoma, histiocytic type											X														
Granulocytic leukemia									X																

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

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	105	105	105	105	105	092	105	105	105	079	105	105	105	096	105	075	105	105	105	095	105	070	105	104	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	−	+	−	−	−	−	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	30
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	−	−	−	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	38
Thymus	−	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	−	+	−	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma	X																									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Squamous cell papilloma																									X	1
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	45
Leiomyosarcoma																										1
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	41
Chromophobe adenoma		X										X														6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																		X								1
Parathyroid	+	+	+	−	+	−	−	+	+	−	+	−	+	−	+	−	−	−	−	+	−	−	+	−	+	+	23
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp		X																								1
Endometrial stromal sarcoma																										1
Hemangioma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
Papillary adenocarcinoma																										1
MUSCULOSKELETAL SYSTEM																										
Muscle	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
Sarcoma, NOS																								X		1
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
Sarcoma, NOS, metastatic																								X		1
Malignant lymphoma, NOS										X				X			X		X		X					5
Malignant lymphoma, histiocytic type																										1
Granulocytic leukemia																										1

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)		2 (4%)
HEMORRHAGE	1 (2%)			
HYPERKERATOSIS	1 (2%)	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)		
FIBROSIS, FOCAL			1 (2%)	
NECROSIS, FAT	1 (2%)			
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(48)	(48)	(49)
HEMORRHAGE			1 (2%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)	1 (2%)
#LUNG	(50)	(50)	(50)	(50)
CONGESTION, NOS				4 (8%)
EDEMA, NOS		1 (2%)	1 (2%)	5 (10%)
HEMORRHAGE	2 (4%)	4 (8%)	5 (10%)	2 (4%)
INFLAMMATION, INTERSTITIAL	3 (6%)	8 (16%)	2 (4%)	3 (6%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
PERIVASCULAR CUFFING		2 (4%)	1 (2%)	
EPITHELIALIZATION	1 (2%)	1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)
HISTIOCYTOSIS	4 (8%)	3 (6%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(50)	(49)	(50)
MYELOFIBROSIS	1 (2%)			
#SPLEEN	(50)	(50)	(50)	(50)
FIBROSIS				1 (2%)
FIBROSIS, MULTIFOCAL		1 (2%)		
NECROSIS, NOS				1 (2%)
INFARCT, NOS			1 (2%)	
HEMATOPOIESIS	1 (2%)			
#MANDIBULAR L. NODE	(50)	(49)	(50)	(48)
EDEMA, NOS		1 (2%)		
HEMORRHAGE	2 (4%)			
DEGENERATION, CYSTIC	4 (8%)	7 (14%)	4 (8%)	1 (2%)
#MEDIASTINAL L. NODE	(50)	(49)	(50)	(48)
HEMORRHAGE	2 (4%)	6 (12%)	7 (14%)	5 (10%)
INFLAMMATION, SUPPURATIVE				1 (2%)
DEGENERATION, CYSTIC	1 (2%)			
HEMOSIDEROSIS		1 (2%)	5 (10%)	
#MESENTERIC L. NODE	(50)	(49)	(50)	(48)
DEGENERATION, CYSTIC			1 (2%)	1 (2%)
#KIDNEY	(50)	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)			
#THYMUS	(38)	(45)	(41)	(41)
PERSISTENT EMBRYONIC STRUCTURE	17 (45%)	25 (56%)	21 (51%)	14 (34%)
ECTOPIA	1 (3%)	2 (4%)	1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*THORACIC CAVITY	(50)	(50)	(50)	(50)
POLYANGIITIS	1 (2%)			
#HEART	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
#HEART/ATRIUM	(50)	(50)	(50)	(50)
THROMBOSIS, NOS			2 (4%)	1 (2%)
FIBROSIS				1 (2%)
#MYOCARDIUM	(50)	(50)	(50)	(50)
FIBROSIS	39 (78%)	34 (68%)	32 (64%)	41 (82%)
DEGENERATION, NOS	2 (4%)	1 (2%)	2 (4%)	1 (2%)
*ASCENDING AORTA	(50)	(50)	(50)	(50)
MINERALIZATION			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
MINERALIZATION	20 (40%)	22 (44%)	21 (42%)	20 (40%)
#SALIVARY GLAND	(50)	(49)	(50)	(49)
EMBOLUS, FOREIGN BODY	1 (2%)			
PERIVASCULITIS	1 (2%)			
#PANCREAS	(50)	(49)	(47)	(47)
POLYANGIITIS		2 (4%)		
DIGESTIVE SYSTEM				
*HARD PALATE	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
#SALIVARY GLAND	(50)	(49)	(50)	(49)
INFLAMMATION, CHRONIC				1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)	
METAPLASIA, SQUAMOUS	1 (2%)			
#LIVER	(50)	(50)	(50)	(50)
ECTOPIA			1 (2%)	
INFLAMMATION, MULTIFOCAL	2 (4%)	1 (2%)	2 (4%)	1 (2%)
FIBROSIS, FOCAL				1 (2%)
CHOLANGIOFIBROSIS	24 (48%)	34 (68%)	24 (48%)	23 (46%)
NECROSIS, NOS	1 (2%)			
NECROSIS, FOCAL		1 (2%)		1 (2%)
METAMORPHOSIS FATTY	2 (4%)	2 (4%)	1 (2%)	1 (2%)
CYTOPLASMIC CHANGE, NOS	1 (2%)	2 (4%)	2 (4%)	2 (4%)
GROUND-GLASS CYTO CHANGE	4 (8%)	3 (6%)	3 (6%)	1 (2%)
EOSINOPHILIC CYTO CHANGE	1 (2%)		2 (4%)	
ANGIECTASIS	1 (2%)	7 (14%)	9 (18%)	14 (28%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	2 (4%)	2 (4%)
#BILE DUCT	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS	36 (72%)	41 (82%)	36 (72%)	36 (72%)
#PANCREAS	(50)	(49)	(47)	(47)
FOCAL CELLULAR CHANGE		3 (6%)	1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREATIC ACINUS	(50)	(49)	(47)	(47)
ATROPHY, NOS	7 (14%)	10 (20%)	9 (19%)	8 (17%)
#PERIESOPHAGEAL TISSUE	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
#FORESTOMACH	(50)	(50)	(50)	(50)
ULCER, NOS		1 (2%)		
INFLAMMATION, ACUTE			1 (2%)	
FIBROSIS		1 (2%)		
#GASTRIC FUNDUS	(50)	(50)	(50)	(50)
ULCER, NOS	1 (2%)		1 (2%)	
EROSION				1 (2%)
#COLON	(50)	(50)	(48)	(48)
PARASITISM				2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)	
POLYCYSTIC KIDNEY	1 (2%)			
HEMORRHAGE	12 (24%)	11 (22%)	7 (14%)	8 (16%)
INFLAMMATION, INTERSTITIAL	1 (2%)			
NEPHROPATHY	50 (100%)	50 (100%)	48 (96%)	44 (88%)
INFARCT, NOS			1 (2%)	
HEMOSIDEROSIS	1 (2%)	1 (2%)	4 (8%)	
#RENAL PAPILLA	(50)	(50)	(50)	(50)
MINERALIZATION		23 (46%)	5 (10%)	3 (6%)
#KIDNEY/TUBULE	(50)	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAMINATION		1 (2%)		
#URINARY BLADDER	(49)	(50)	(49)	(50)
DILATATION, NOS			1 (2%)	
HEMORRHAGE	2 (4%)	2 (4%)		
INFLAMMATION, SUPPURATIVE	1 (2%)			
NECROSIS, HEMORRHAGIC			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(50)	(50)	(48)	(50)
CYST, NOS			1 (2%)	
#ANTERIOR PITUITARY	(50)	(50)	(48)	(50)
CYST, NOS	1 (2%)	2 (4%)	2 (4%)	
HEMORRHAGE	1 (2%)			
HEMOSIDEROSIS				1 (2%)
FOCAL CELLULAR CHANGE	7 (14%)	5 (10%)	3 (6%)	5 (10%)
ANGIECTASIS	4 (8%)	3 (6%)		
#ADRENAL	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
INFLAMMATION, SUPPURATIVE				1 (2%)
DEGENERATION, LIPOID	1 (2%)			
LIPOIDOSIS	1 (2%)	2 (4%)		
ANGIECTASIS	1 (2%)			2 (4%)
#ADRENAL CORTEX	(49)	(50)	(50)	(50)
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(49)	(50)	(50)	(50)
FOCAL CELLULAR CHANGE	4 (8%)	2 (4%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	8 (16%)	5 (10%)	3 (6%)
#THYROID	(50)	(48)	(48)	(49)
ULTIMOBRANCHIAL CYST	3 (6%)		1 (2%)	1 (2%)
CYSTIC FOLLICLES			3 (6%)	2 (4%)
FOLLICULAR CYST, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
HYPERPLASIA, C-CELL	4 (8%)	11 (23%)	3 (6%)	3 (6%)
#PARATHYROID	(43)	(40)	(38)	(45)
HYPERPLASIA, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)			1 (2%)
GALACTOCELE	1 (2%)	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)			
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, FOCAL				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)		1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
ABSCESS, NOS	3 (6%)	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		1 (2%)
#PROSTATE	(48)	(45)	(49)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, SUPPURATIVE			1 (2%)	1 (2%)
ABSCESS, NOS	1 (2%)			
INFLAMMATION, CHRONIC	5 (10%)	8 (18%)	7 (14%)	10 (21%)
HYPERPLASIA, EPITHELIAL	8 (17%)	13 (29%)	11 (22%)	9 (19%)
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
#TESTIS	(50)	(50)	(50)	(49)
MINERALIZATION	16 (32%)	17 (34%)	16 (32%)	14 (29%)
GRANULOMA, SPERMATIC		1 (2%)		
HYPOSPERMATOGENESIS	2 (4%)	5 (10%)	3 (6%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	7 (14%)	10 (20%)	12 (24%)	3 (6%)
*EPIDIDYMIS	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	4 (8%)	1 (2%)	1 (2%)	1 (2%)
METAPLASIA, NOS		1 (2%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
#BRAIN	(50)	(50)	(50)	(50)
HEMORRHAGE	2 (4%)	2 (4%)	1 (2%)	
STATUS SPONGIOSUS				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
HEMORRHAGE	2 (4%)			1 (2%)
CATARACT	7 (14%)	7 (14%)	8 (16%)	5 (10%)
*EYE/SCLERA	(50)	(50)	(50)	(50)
MINERALIZATION	2 (4%)	7 (14%)	2 (4%)	6 (12%)
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)		
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	8 (16%)	7 (14%)	7 (14%)	5 (10%)
MUSCULOSKELETAL SYSTEM				
*CARTILAGE,NOS	(50)	(50)	(50)	(50)
NECROSIS, NOS	5 (10%)	6 (12%)	16 (32%)	7 (14%)
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
HEMATOMA, NOS			1 (2%)	
ABSCESS, NOS		1 (2%)		
NECROSIS, FAT		3 (6%)	1 (2%)	3 (6%)
*EPICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)		
FOREIGN MATERIAL, NOS		1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(49)	(50)
NECROSIS, FAT	1 (2%)			1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(49)	(48)	(48)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
#LUNG	(50)	(50)	(49)	(50)
CALCULUS,MICROSCOPIC EXAMINATION			1 (2%)	
CONGESTION, NOS	3 (6%)	2 (4%)		6 (12%)
EDEMA, NOS		2 (4%)		7 (14%)
HEMORRHAGE	1 (2%)	5 (10%)	2 (4%)	4 (8%)
BRONCHOPNEUMONIA, NOS			1 (2%)	
INFLAMMATION, INTERSTITIAL	10 (20%)	4 (8%)	4 (8%)	3 (6%)
INFLAMMATION, NECROTIZING	1 (2%)			
INFLAMMATION, GRANULOMATOUS			1 (2%)	1 (2%)
PERIVASCULAR CUFFING		2 (4%)	1 (2%)	
HEMOSIDEROSIS	1 (2%)			1 (2%)
EPITHELIALIZATION		1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(49)	(50)
HISTIOCYTOSIS	7 (14%)	9 (18%)	8 (16%)	7 (14%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(47)	(49)	(49)	(48)
ATROPHY, NOS				1 (2%)
HISTIOCYTOSIS				1 (2%)
MYELOFIBROSIS	1 (2%)	1 (2%)		
#SPLEEN	(50)	(50)	(49)	(49)
FIBROSIS	2 (4%)			1 (2%)
NECROSIS, NOS	1 (2%)			1 (2%)
#SPLENIC CAPSULE	(50)	(50)	(49)	(49)
FIBROSIS				1 (2%)
NECROSIS, NOS			1 (2%)	
#MANDIBULAR L. NODE	(50)	(50)	(49)	(48)
DEGENERATION, CYSTIC	1 (2%)	3 (6%)	1 (2%)	1 (2%)
NECROSIS, NOS	1 (2%)			
#CERVICAL LYMPH NODE	(50)	(50)	(49)	(48)
HISTIOCYTOSIS	1 (2%)			
#MEDIASTINAL L. NODE	(50)	(50)	(49)	(48)
HEMORRHAGE	8 (16%)	9 (18%)	10 (20%)	7 (15%)
HEMOSIDEROSIS	3 (6%)	5 (10%)	3 (6%)	
HISTIOCYTOSIS		1 (2%)		
#PANCREATIC L. NODE	(50)	(50)	(49)	(48)
HEMORRHAGE	1 (2%)			
#RENAL LYMPH NODE	(50)	(50)	(49)	(48)
HISTIOCYTOSIS	1 (2%)			
#THYMUS	(44)	(41)	(47)	(44)
PERSISTENT EMBRYONIC STRUCTURE	21 (48%)	29 (71%)	22 (47%)	19 (43%)
ECTOPIA		1 (2%)		
HEMORRHAGE				2 (5%)
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
POLYANGIITIS		1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#HEART	(50)	(50)	(49)	(50)
HEMORRHAGE				1 (2%)
ARTERIOSCLEROSIS, NOS		1 (2%)	1 (2%)	
FIBROELASTOSIS, NOS			1 (2%)	
#HEART/ATRIUM	(50)	(50)	(49)	(50)
THROMBOSIS, NOS			1 (2%)	
#MYOCARDIUM	(50)	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
INFLAMMATION, ACUTE		1 (2%)		
EOSINOPHILIC INFILTRATE				1 (2%)
INFLAMMATION, GRANULOMATOUS				1 (2%)
FIBROSIS	17 (34%)	15 (30%)	18 (37%)	16 (32%)
DEGENERATION, NOS	2 (4%)	1 (2%)	1 (2%)	3 (6%)
*PULMONARY ARTERY	(50)	(50)	(49)	(50)
MINERALIZATION	16 (32%)	15 (30%)	8 (16%)	14 (28%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(49)	(49)
CALCULUS,UNKN GROSS OR MICRO				1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
#LIVER	(50)	(50)	(49)	(50)
ECTOPIA	2 (4%)			
DILATATION/DUCTS			1 (2%)	
HEMORRHAGE				1 (2%)
INFLAMMATION, MULTIFOCAL	20 (40%)	15 (30%)	16 (33%)	9 (18%)
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, GRANULOMATOUS				1 (2%)
CHOLANGIOFIBROSIS	10 (20%)	9 (18%)	9 (18%)	15 (30%)
NECROSIS, NOS				1 (2%)
NECROSIS, FOCAL		1 (2%)	1 (2%)	
NECROSIS, COAGULATIVE	1 (2%)			
METAMORPHOSIS FATTY	2 (4%)	2 (4%)		1 (2%)
CYTOPLASMIC CHANGE, NOS	1 (2%)		2 (4%)	3 (6%)
BASOPHILIC CYTO CHANGE			1 (2%)	
GROUND-GLASS CYTO CHANGE	2 (4%)	2 (4%)	3 (6%)	2 (4%)
EOSINOPHILIC CYTO CHANGE		1 (2%)		
ANGIECTASIS			3 (6%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)	(50)
NECROSIS, NOS		1 (2%)	1 (2%)	
METAMORPHOSIS FATTY		1 (2%)		1 (2%)
#LIVER/PERIPORTAL	(50)	(50)	(49)	(50)
METAMORPHOSIS FATTY		1 (2%)	2 (4%)	
#BILE DUCT	(50)	(50)	(49)	(50)
CHOLANGIOFIBROSIS				2 (4%)
HYPERPLASIA, NOS	10 (20%)	15 (30%)	16 (33%)	10 (20%)
#PANCREAS	(50)	(49)	(48)	(49)
NECROSIS, NOS			1 (2%)	
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		
#PANCREATIC ACINUS	(50)	(49)	(48)	(49)
ATROPHY, NOS	7 (14%)	7 (14%)	6 (13%)	5 (10%)
#ESOPHAGUS	(49)	(50)	(49)	(49)
ULCER, NOS			1 (2%)	
GRANULOMA, NOS			1 (2%)	
#FORESTOMACH	(50)	(50)	(48)	(49)
ULCER, NOS	1 (2%)	1 (2%)		
INFLAMMATION, CHRONIC				2 (4%)
HYPERPLASIA, EPITHELIAL				1 (2%)
#PYLORUS	(50)	(50)	(48)	(49)
EROSION				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#COLON	(50)	(48)	(48)	(49)
PARASITISM	1 (2%)			1 (2%)
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(49)	(50)
CALCULUS,UNKN GROSS OR MICRO			2 (4%)	
CALCULUS,MICROSCOPIC EXAMINATION		1 (2%)		2 (4%)
HYDRONEPHROSIS		1 (2%)		
HEMORRHAGE	7 (14%)	9 (18%)	11 (22%)	8 (16%)
FIBROSIS, DIFFUSE		1 (2%)		
NEPHROPATHY	29 (58%)	33 (66%)	34 (69%)	29 (58%)
METAMORPHOSIS FATTY		2 (4%)		
HEMOSIDEROSIS	1 (2%)	3 (6%)	3 (6%)	2 (4%)
CYTOPLASMIC VACUOLIZATION			1 (2%)	
#RENAL PAPILLA	(50)	(50)	(49)	(50)
MINERALIZATION			2 (4%)	1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(49)	(50)
CALCULUS,UNKN GROSS OR MICRO		1 (2%)		
CALCULUS,MICROSCOPIC EXAMINATION	1 (2%)	1 (2%)	2 (4%)	2 (4%)
MINERALIZATION	9 (18%)		3 (6%)	
#URINARY BLADDER	(49)	(48)	(48)	(50)
HEMORRHAGE		1 (2%)		
HEMOSIDEROSIS			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(50)	(50)	(46)	(50)
HEMORRHAGE	1 (2%)			
CYTOMEGALY			1 (2%)	
#ANTERIOR PITUITARY	(50)	(50)	(46)	(50)
CYST, NOS	7 (14%)	10 (20%)	4 (9%)	7 (14%)
HEMORRHAGE		2 (4%)	1 (2%)	
HEMOSIDEROSIS				2 (4%)
FOCAL CELLULAR CHANGE	6 (12%)		3 (7%)	2 (4%)
ANGIECTASIS	10 (20%)	3 (6%)	8 (17%)	3 (6%)
#ADRENAL	(50)	(50)	(49)	(50)
DEGENERATION, LIPOID	3 (6%)			
LIPOIDOSIS		3 (6%)	2 (4%)	2 (4%)
ANGIECTASIS	3 (6%)	2 (4%)	1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(49)	(50)
PIGMENTATION, NOS			1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)	
ATROPHY, NOS		1 (2%)	1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(49)	(50)
FIBROSIS				1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)			
HYPERPLASIA, FOCAL		1 (2%)		
#THYROID	(50)	(50)	(49)	(48)
ULTIMOBRANCHIAL CYST	1 (2%)	1 (2%)	1 (2%)	1 (2%)
CYSTIC FOLLICLES		1 (2%)		
HYPERPLASIA, C-CELL	6 (12%)	6 (12%)	5 (10%)	2 (4%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)		
#PARATHYROID	(44)	(43)	(33)	(39)
ECTOPIA	1 (2%)			

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(49)	(50)
DILATATION/DUCTS	2 (4%)	1 (2%)		
GALACTOCELE	1 (2%)	1 (2%)	1 (2%)	2 (4%)
FIBROSIS, FOCAL				1 (2%)
HYPERPLASIA, NODULAR	1 (2%)			
*PREPUTIAL GLAND	(50)	(50)	(49)	(50)
ABSCESS, NOS		1 (2%)		
*CLITORAL GLAND	(50)	(50)	(49)	(50)
DILATATION/DUCTS	1 (2%)	1 (2%)		
ABSCESS, NOS			1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
*VAGINA	(50)	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
#UTERUS	(50)	(50)	(49)	(50)
HEMORRHAGE	1 (2%)			
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)	(50)
CYST, NOS	1 (2%)		1 (2%)	1 (2%)
#OVARY	(50)	(50)	(48)	(50)
CYST, NOS			1 (2%)	
FOLLICULAR CYST, NOS			1 (2%)	
PAROVARIAN CYST	4 (8%)	4 (8%)	4 (8%)	2 (4%)
NECROSIS, NOS	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(49)	(50)
DISPLACEMENT, NOS			1 (2%)	
HEMORRHAGE	1 (2%)	2 (4%)	2 (4%)	2 (4%)
MALACIA			1 (2%)	
#BRAIN STEM	(50)	(50)	(49)	(50)
DISPLACEMENT, NOS				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(49)	(50)
RETINOPATHY				1 (2%)
CATARACT	8 (16%)	7 (14%)	5 (10%)	8 (16%)
PHTHISIS BULBI		1 (2%)		1 (2%)
*EYE POSTERIOR CHAMBER	(50)	(50)	(49)	(50)
HEMORRHAGE		1 (2%)		
*EYE/SCLERA	(50)	(50)	(49)	(50)
MINERALIZATION	2 (4%)	1 (2%)	1 (2%)	2 (4%)
*EYE/CORNEA	(50)	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)		
*EYE/RETINA	(50)	(50)	(49)	(50)
DEGENERATION, NOS	7 (14%)	8 (16%)	5 (10%)	8 (16%)
*HARDERIAN GLAND	(50)	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM				
*STERNUM	(50)	(50)	(49)	(50)
NECROSIS, NOS	4 (8%)			
OSTEOSCLEROSIS	3 (6%)		4 (8%)	1 (2%)
*CARTILAGE, NOS	(50)	(50)	(49)	(50)
NECROSIS, NOS		4 (8%)	6 (12%)	6 (12%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*THORACIC CAVITY	(50)	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
*MEDIASTINUM	(50)	(50)	(49)	(50)
HEMORRHAGE	1 (2%)			
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)		
NECROSIS, FAT		1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(49)	(50)
NECROSIS, FAT	3 (6%)	2 (4%)	2 (4%)	3 (6%)
*PLEURA	(50)	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)		
FOREIGN MATERIAL, NOS		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
HEMORRHAGE			1 (2%)	
INFLAMMATION, NOS	1 (2%)			
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSEXED/NO NECROPSY			1	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	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)
ULCER, NOS	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	2 (4%)
FIBROSIS		1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		
GRANULOMA, NOS		1 (2%)	
INFLAMMATION, NECRO GRANULOMATOUS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE	4 (8%)	3 (6%)	8 (16%)
*NASAL GLAND	(50)	(50)	(50)
INFLAMMATION, ACUTE			3 (6%)
#TRACHEA	(27)	(30)	(28)
INFLAMMATION, ACUTE			1 (4%)
#LUNG	(50)	(50)	(50)
ASPIRATION, NOS		1 (2%)	
MINERALIZATION	1 (2%)		
CONGESTION, NOS		2 (4%)	2 (4%)
HEMORRHAGE	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	3 (6%)	1 (2%)
HISTIOCYTOSIS	2 (4%)	3 (6%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMOID REACTION		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	3 (6%)	1 (2%)
HEMATOPOIESIS		3 (6%)	3 (6%)
*SUBCUT TISSUE	(50)	(50)	(50)
MASTOCYTOSIS	1 (2%)		
#BONE MARROW	(50)	(49)	(49)
ANGIECTASIS			1 (2%)
#SPLEEN	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)		
ANGIECTASIS			2 (4%)
HEMATOPOIESIS	5 (10%)	4 (8%)	5 (10%)
#MANDIBULAR L. NODE	(45)	(47)	(47)
PLASMACYTOSIS		2 (4%)	
HYPERPLASIA, LYMPHOID			1 (2%)
MASTOCYTOSIS	1 (2%)		
#BRONCHIAL LYMPH NODE	(45)	(47)	(47)
HYPERPLASIA, LYMPHOID			1 (2%)
#MEDIASTINAL L. NODE	(45)	(47)	(47)
EDEMA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#MESENTERIC L. NODE	(45)	(47)	(47)
HEMORRHAGE	25 (56%)	28 (60%)	24 (51%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
ANGIECTASIS	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (4%)		1 (2%)
HEMATOPOIESIS		3 (6%)	2 (4%)
#RENAL LYMPH NODE	(45)	(47)	(47)
DILATATION/SINUS			1 (2%)
*STERNUM	(50)	(50)	(50)
MASTOCYTOSIS		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS		1 (2%)	
#JEJUNUM	(48)	(50)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#ILEUM	(48)	(50)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(41)	(40)	(46)
CYST, NOS	6 (15%)	8 (20%)	11 (24%)
MULTIPLE CYSTS		1 (3%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
#HEART	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE			2 (4%)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS			1 (2%)
ANGIECTASIS			1 (2%)
#HEART/ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#CARDIAC VALVE	(50)	(50)	(50)
PIGMENTATION, NOS	1 (2%)	2 (4%)	4 (8%)
*BLOOD VESSEL	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#PANCREAS	(50)	(50)	(50)
PERIVASCULITIS			1 (2%)
DIGESTIVE SYSTEM			
*HARD PALATE	(50)	(50)	(50)
FIBROSIS		1 (2%)	
*LIP	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*TOOTH	(50)	(50)	(50)
INFLAMMATION, ACUTE		3 (6%)	2 (4%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
GROWTH, ALTERATION			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#SALIVARY GLAND	(50)	(50)	(50)
MINERALIZATION	3 (6%)	1 (2%)	1 (2%)
DILATATION/DUCTS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
ATROPHY, NOS	2 (4%)	2 (4%)	1 (2%)
#LIVER	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
ABNORMAL CURVATURE			1 (2%)
CYST, NOS			2 (4%)
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
NECROSIS, NOS		2 (4%)	3 (6%)
NECROSIS, COAGULATIVE	1 (2%)	1 (2%)	
CYTOPLASMIC VACUOLIZATION	23 (46%)	21 (42%)	30 (60%)
BASOPHILIC CYTO CHANGE	2 (4%)	3 (6%)	2 (4%)
FOCAL CELLULAR CHANGE			1 (2%)
EOSINOPHILIC CYTO CHANGE		1 (2%)	
CLEAR-CELL CHANGE	8 (16%)	12 (24%)	14 (28%)
HEPATOCYTOMEGALY	1 (2%)	1 (2%)	2 (4%)
ANGIECTASIS		1 (2%)	1 (2%)
*GALLBLADDER	(50)	(50)	(50)
CYST, NOS		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(50)	(50)	(50)
ECTOPIA	1 (2%)		
DILATATION/DUCTS		1 (2%)	
CYST, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	
#PANCREATIC ACINUS	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	4 (8%)	4 (8%)
ATROPHY, NOS	3 (6%)	6 (12%)	4 (8%)
#STOMACH	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#GASTRIC FUNDAL GLAND	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
#GLANDULAR STOMACH	(50)	(50)	(50)
MINERALIZATION		1 (2%)	3 (6%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	1 (2%)
#STOMACH WALL	(50)	(50)	(50)
MINERALIZATION			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)	3 (6%)	
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	1 (2%)
#ILEUM	(48)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	10 (20%)	8 (16%)	6 (12%)
HYDRONEPHROSIS	1 (2%)		
CYST, NOS	1 (2%)	2 (4%)	4 (8%)
CONGESTION, NOS			1 (2%)
GLOMERULONEPHRITIS, NOS		1 (2%)	3 (6%)
PYELONEPHRITIS, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	9 (18%)	3 (6%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
NEPHROSIS, NOS	18 (36%)	15 (30%)	19 (38%)
INFARCT, NOS	1 (2%)	1 (2%)	5 (10%)
METAPLASIA, OSSEOUS	2 (4%)		
#PERIRENAL TISSUE	(50)	(50)	(50)
GRANULOMA, NOS		1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#URINARY BLADDER	(50)	(47)	(50)
CALCULUS,GROSS OBSERVATION ONLY	1 (2%)		
DILATATION, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(48)	(47)	(48)
CYST, NOS			1 (2%)
COLLOID CYST		1 (2%)	
CONGESTION, NOS	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)		
#ADRENAL/CAPSULE	(50)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	7 (14%)	6 (12%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)	1 (2%)	
CLEAR-CELL CHANGE	4 (8%)	3 (6%)	5 (10%)
ATROPHY, BROWN	1 (2%)	4 (8%)	1 (2%)
HYPERTROPHY, FOCAL	8 (16%)	4 (8%)	6 (12%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
AMYLOIDOSIS	1 (2%)		1 (2%)
HYPERPLASIA, NOS	6 (12%)	9 (18%)	7 (14%)
HYPERPLASIA, FOCAL		2 (4%)	
#THYROID	(49)	(50)	(47)
FOLLICULAR CYST, NOS	13 (27%)	10 (20%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	1 (2%)	1 (2%)
#PARATHYROID	(37)	(23)	(24)
CYST, NOS			1 (4%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION, NOS	2 (4%)		
DILATATION/DUCTS	1 (2%)		2 (4%)
CYST, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
ABSCESS, NOS	4 (8%)	5 (10%)	5 (10%)
INFLAMMATION, ACUTE/CHRONIC	3 (6%)		2 (4%)
INFLAMMATION, CHRONIC	2 (4%)	2 (4%)	1 (2%)
#PROSTATE	(50)	(50)	(50)
HEMORRHAGE	3 (6%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
*COAGULATING GLAND	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#TESTIS	(50)	(50)	(49)
MINERALIZATION	17 (34%)	17 (34%)	11 (22%)
NECROSIS, FAT	1 (2%)		
ATROPHY, NOS	1 (2%)	3 (6%)	2 (4%)
ANGIECTASIS		1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
GRANULOMA, SPERMATIC	1 (2%)	1 (2%)	
FIBROSIS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
MINERALIZATION	16 (32%)	18 (36%)	20 (40%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
CYTOPLASMIC VACUOLIZATION		2 (4%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
COLLAPSE	1 (2%)		
*EUSTACHIAN TUBE	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	3 (6%)
INFLAMMATION, ACUTE		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	2 (4%)
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (10%)	9 (18%)	11 (22%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFECTION, BACTERIAL	1 (2%)		
NECROSIS, NOS	2 (4%)		
NECROSIS, FAT		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		3	
ANIMALS NECROPSIED	50	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	47	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(47)	(50)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
ULCERATION, DIFFUSE			1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS	1 (2%)		
HYPERKERATOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(47)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#BRONCHIAL CARTILAGE	(50)	(46)	(50)
MINERALIZATION		1 (2%)	
#LUNG	(50)	(46)	(50)
BRONCHIECTASIS	1 (2%)	1 (2%)	
EDEMA, NOS			1 (2%)
HEMORRHAGE	3 (6%)	2 (4%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
HISTIOCYTOSIS	5 (10%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(50)
LEUKEMOID REACTION			1 (2%)
HYPERPLASIA, LYMPHOID	3 (6%)	9 (19%)	2 (4%)
HEMATOPOIESIS	1 (2%)		2 (4%)
MYELOPOIESIS			1 (2%)
#BONE MARROW	(50)	(47)	(49)
MYELOSCLEROSIS	41 (82%)	38 (81%)	30 (61%)
#SPLEEN	(49)	(47)	(49)
HEMOSIDEROSIS	9 (18%)	5 (11%)	3 (6%)
HYPERPLASIA, LYMPHOID	2 (4%)	4 (9%)	2 (4%)
HEMATOPOIESIS	2 (4%)	3 (6%)	3 (6%)
#MANDIBULAR L. NODE	(32)	(34)	(38)
EDEMA, NOS	1 (3%)		
HYPERPLASIA, LYMPHOID			4 (11%)
#MEDIASTINAL L. NODE	(32)	(34)	(38)
EDEMA, NOS	1 (3%)		
#PANCREATIC L. NODE	(32)	(34)	(38)
CONGESTION, NOS		1 (3%)	
#MESENTERIC L. NODE	(32)	(34)	(38)
HEMORRHAGE			4 (11%)
ANGIECTASIS			1 (3%)
HYPERPLASIA, LYMPHOID	1 (3%)	1 (3%)	
#RENAL LYMPH NODE	(32)	(34)	(38)
HYPERPLASIA, LYMPHOID			1 (3%)
#LIVER	(50)	(47)	(49)
HEMATOPOIESIS	1 (2%)		
#PEYER'S PATCH	(50)	(44)	(45)
HYPERPLASIA, LYMPHOID		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#JEJUNUM	(50)	(44)	(45)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	3 (7%)
#THYMUS	(44)	(39)	(39)
CYST, NOS	8 (18%)	8 (21%)	6 (15%)
MULTIPLE CYSTS		1 (3%)	1 (3%)
CONGESTION, NOS	1 (2%)		
LYMPHOID DEPLETION	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)	1 (3%)	1 (3%)
#THYMIC LYMPHOCYTES	(44)	(39)	(39)
NECROSIS, NOS			1 (3%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(50)
THROMBOSIS, NOS		1 (2%)	
#SPLEEN	(49)	(47)	(49)
THROMBOSIS, NOS	1 (2%)		
#HEART	(50)	(47)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS	1 (2%)		
DEGENERATION, NOS	1 (2%)		
#HEART/ATRIUM	(50)	(47)	(50)
THROMBOSIS, NOS	1 (2%)		
#CARDIAC VALVE	(50)	(47)	(50)
PIGMENTATION, NOS			1 (2%)
*BLOOD VESSEL	(50)	(47)	(50)
INFLAMMATION, FIBRINOID	1 (2%)		
*AORTA	(50)	(47)	(50)
MINERALIZATION		1 (2%)	
*THYMIC ARTERY	(50)	(47)	(50)
INFLAMMATION, FIBRINOID		1 (2%)	
*PULMONARY VEIN	(50)	(47)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
#UTERUS	(50)	(47)	(49)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(47)	(49)
ATROPHY, NOS	1 (2%)		1 (2%)
#LIVER	(50)	(47)	(49)
CYST, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE	1 (2%)	2 (4%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, NOS			1 (2%)
NECROSIS, NOS	1 (2%)	2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	34 (68%)	39 (83%)	29 (59%)
BASOPHILIC CYTO CHANGE	1 (2%)		
EOSINOPHILIC CYTO CHANGE			1 (2%)
CLEAR-CELL CHANGE	14 (28%)	7 (15%)	5 (10%)
HEPATOCYTOMEGALY		2 (4%)	
HYPOPLASIA, NOS	1 (2%)		
ANGIECTASIS			1 (2%)
*GALLBLADDER	(50)	(47)	(50)
INFLAMMATION, ACUTE NECROTIZING	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
PIGMENTATION, NOS	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREAS	(50)	(47)	(48)
DILATATION/DUCTS	1 (2%)	1 (2%)	
CYST, NOS		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#PANCREATIC ACINUS	(50)	(47)	(48)
CYTOPLASMIC VACUOLIZATION			1 (2%)
HYPOPLASIA, NOS		1 (2%)	
ATROPHY, NOS	1 (2%)	4 (9%)	3 (6%)
HYPERPLASIA, NOS		1 (2%)	
#PERIPANCREATIC TISSUE	(50)	(47)	(48)
NECROSIS, FAT			1 (2%)
#STOMACH	(50)	(47)	(46)
MINERALIZATION	1 (2%)		
CYST, NOS			1 (2%)
EDEMA, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)	2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
NECROSIS, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#GASTRIC FUNDAL GLAND	(50)	(47)	(46)
DILATATION, NOS	2 (4%)	2 (4%)	
#JEJUNUM	(50)	(44)	(45)
ULCER, NOS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(47)	(49)
HYDRONEPHROSIS	1 (2%)		
GLOMERULONEPHRITIS, NOS	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (4%)
NEPHROSIS, NOS	7 (14%)	5 (11%)	7 (14%)
NECROSIS, NOS			1 (2%)
INFARCT, NOS	1 (2%)	2 (4%)	3 (6%)
METAPLASIA, OSSEOUS	3 (6%)	3 (6%)	3 (6%)
#KIDNEY/TUBULE	(50)	(47)	(49)
PIGMENTATION, NOS	1 (2%)		
*PERIURETERAL TISSUE	(50)	(47)	(50)
STEATITIS			1 (2%)
#URINARY BLADDER	(46)	(47)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(46)	(41)
COLLOID CYST	1 (2%)		
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	10 (20%)	8 (17%)	5 (12%)
ANGIECTASIS	1 (2%)	2 (4%)	
#ADRENAL	(50)	(47)	(50)
CYST, NOS			1 (2%)
CONGESTION, NOS	1 (2%)		1 (2%)
ANGIECTASIS	1 (2%)		
#ADRENAL/CAPSULE	(50)	(47)	(50)
HYPERPLASIA, NOS		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL CORTEX	(50)	(47)	(50)
CYST, NOS			1 (2%)
DEGENERATION, BALLOONING	1 (2%)		1 (2%)
PIGMENTATION, NOS	1 (2%)		
ATROPHY, BROWN	32 (64%)	35 (74%)	32 (64%)
HYPERTROPHY, FOCAL	5 (10%)	2 (4%)	5 (10%)
HYPERPLASIA, NODULAR	2 (4%)		
#ADRENAL MEDULLA	(50)	(47)	(50)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	2 (4%)
#THYROID	(45)	(47)	(45)
THYROGLOSSAL DUCT CYST	1 (2%)		
FOLLICULAR CYST, NOS	5 (11%)	5 (11%)	12 (27%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	6 (13%)	9 (19%)	3 (7%)
#PARATHYROID	(24)	(26)	(23)
CYST, NOS	1 (4%)	2 (8%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(47)	(50)
DILATATION/DUCTS		1 (2%)	
HYPERPLASIA, NOS	4 (8%)	3 (6%)	3 (6%)
LACTATION	1 (2%)		1 (2%)
#UTERUS	(50)	(47)	(49)
HYDROMETRA	1 (2%)	1 (2%)	2 (4%)
ANGIECTASIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(47)	(49)
CYST, NOS	10 (20%)	5 (11%)	5 (10%)
MULTIPLE CYSTS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	38 (76%)	38 (81%)	34 (69%)
#OVARY	(49)	(45)	(48)
MINERALIZATION	1 (2%)		1 (2%)
CYST, NOS	13 (27%)	13 (29%)	9 (19%)
HEMORRHAGIC CYST	2 (4%)	3 (7%)	
ATROPHY, NOS		1 (2%)	
ANGIECTASIS	1 (2%)		
#MESOVARIUM	(49)	(45)	(48)
CYST, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
NECROSIS, FAT		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(47)	(50)
MINERALIZATION	20 (40%)	17 (36%)	24 (48%)
#HIPPOCAMPUS	(50)	(47)	(50)
NECROSIS, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(47)	(50)
COLLAPSE			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(50)	(47)	(50)
NECROSIS, FAT	1 (2%)		2 (4%)
*MESENTERY	(50)	(47)	(50)
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(50)
MINERALIZATION			1 (2%)
CONGESTION, NOS	1 (2%)	1 (2%)	6 (12%)
LYMPHOCYTIC INFLAMMATORY INFILTR	25 (50%)	28 (60%)	30 (60%)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
BACTERIAL SEPTICEMIA			1 (2%)
NECROSIS, FAT			1 (2%)
TAIL			
FIBROUS OSTEODYSTROPHY	1		
UTERINE LIGAMENT			
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY		3	

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Skin: Squamous Cell Papilloma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	2.6%	2.6%	3.6%	15.0%
Terminal Rates (c)	1/38 (3%)	1/38 (3%)	1/28 (4%)	3/23 (13%)
Life Table Tests (d)	P=0.020	P=0.762	P=0.692	P=0.081
Incidental Tumor Tests (d)	P=0.025	P=0.762	P=0.692	P=0.098
Cochran-Armitage Trend Test (d)	P=0.067			
Fisher Exact Test		P=0.753	P=0.753	P=0.181
Skin: Fibroma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.3%	3.6%	0.0%
Terminal Rates (c)	0/38 (0%)	1/38 (3%)	1/28 (4%)	0/23 (0%)
Life Table Tests (d)	P=0.480N	P=0.124	P=0.439	(e)
Incidental Tumor Tests (d)	P=0.293N	P=0.107	P=0.439	(e)
Cochran-Armitage Trend Test (d)	P=0.366N			
Fisher Exact Test		P=0.121	P=0.500	(e)
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	7.3%	7.9%	13.6%	4.3%
Terminal Rates (c)	2/38 (5%)	3/38 (8%)	3/28 (11%)	1/23 (4%)
Life Table Tests (d)	P=0.462N	P=0.662	P=0.367	P=0.448N
Incidental Tumor Tests (d)	P=0.345N	P=0.662	P=0.474	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.248N			
Fisher Exact Test		P=0.661	P=0.500	P=0.309N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	7.3%	10.1%	13.6%	4.3%
Terminal Rates (c)	2/38 (5%)	3/38 (8%)	3/28 (11%)	1/23 (4%)
Life Table Tests (d)	P=0.406N	P=0.496	P=0.367	P=0.448N
Incidental Tumor Tests (d)	P=0.275N	P=0.500	P=0.474	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.210N			
Fisher Exact Test		P=0.500	P=0.500	P=0.309N
Integumentary System: Fibroma				
Overall Rates (a)	3/50 (6%)	6/50 (12%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	7.3%	14.8%	17.1%	4.3%
Terminal Rates (c)	2/38 (5%)	4/38 (11%)	4/28 (14%)	1/23 (4%)
Life Table Tests (d)	P=0.383N	P=0.248	P=0.229	P=0.448N
Incidental Tumor Tests (d)	P=0.204N	P=0.229	P=0.312	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.170N			
Fisher Exact Test		P=0.243	P=0.357	P=0.309N
Integumentary System: Fibroma or Fibrosarcoma				
Overall Rates (a)	3/50 (6%)	7/50 (14%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	7.3%	16.9%	17.1%	4.3%
Terminal Rates (c)	2/38 (5%)	4/38 (11%)	4/28 (14%)	1/23 (4%)
Life Table Tests (d)	P=0.339N	P=0.165	P=0.229	P=0.448N
Incidental Tumor Tests (d)	P=0.161N	P=0.146	P=0.312	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.145N			
Fisher Exact Test		P=0.159	P=0.357	P=0.309N
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	14/50 (28%)	21/50 (42%)	19/50 (38%)	25/50 (50%)
Adjusted Rates (b)	30.7%	49.6%	47.3%	63.4%
Terminal Rates (c)	7/38 (18%)	17/38 (45%)	8/28 (29%)	10/23 (43%)
Life Table Tests (d)	P=0.001	P=0.123	P=0.088	P=0.003
Incidental Tumor Tests (d)	P=0.127	P=0.082	P=0.440	P=0.127
Cochran-Armitage Trend Test (d)	P=0.027			
Fisher Exact Test		P=0.104	P=0.198	P=0.020

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Liver: Neoplastic Nodule				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.3%	7.9%	10.7%	9.1%
Terminal Rates (c)	0/38 (0%)	3/38 (8%)	3/28 (11%)	1/23 (4%)
Life Table Tests (d)	P=0.146	P=0.303	P=0.224	P=0.243
Incidental Tumor Tests (d)	P=0.204	P=0.307	P=0.255	P=0.380
Cochran-Armitage Trend Test (d)	P=0.292			
Fisher Exact Test		P=0.309	P=0.309	P=0.309
Pituitary: Adenoma				
Overall Rates (a)	7/50 (14%)	4/50 (8%)	7/48 (15%)	0/50 (0%)
Adjusted Rates (b)	16.9%	10.5%	20.5%	0.0%
Terminal Rates (c)	5/38 (13%)	4/38 (11%)	3/27 (11%)	0/23 (0%)
Life Table Tests (d)	P=0.071N	P=0.264N	P=0.425	P=0.030N
Incidental Tumor Tests (d)	P=0.018N	P=0.262N	P=0.574N	P=0.017N
Cochran-Armitage Trend Test (d)	P=0.019N			
Fisher Exact Test		P=0.262N	P=0.581	P=0.006N
Adrenal: Pheochromocytoma				
Overall Rates (a)	9/49 (18%)	16/50 (32%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	22.6%	40.0%	31.8%	19.3%
Terminal Rates (c)	8/38 (21%)	14/38 (37%)	8/28 (29%)	4/23 (17%)
Life Table Tests (d)	P=0.359N	P=0.082	P=0.259	P=0.500N
Incidental Tumor Tests (d)	P=0.227N	P=0.072	P=0.333	P=0.454N
Cochran-Armitage Trend Test (d)	P=0.055N			
Fisher Exact Test		P=0.091	P=0.520	P=0.183N
Thyroid: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	2/50 (4%)	0/48 (0%)	4/48 (8%)	1/49 (2%)
Adjusted Rates (b)	4.8%	0.0%	14.8%	3.4%
Terminal Rates (c)	1/38 (3%)	0/38 (0%)	4/27 (15%)	0/23 (0%)
Life Table Tests (d)	P=0.455	P=0.245N	P=0.212	P=0.599N
Incidental Tumor Tests (d)	P=0.594	P=0.240N	P=0.228	P=0.368N
Cochran-Armitage Trend Test (d)	P=0.582N			
Fisher Exact Test		P=0.258N	P=0.319	P=0.508N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	4/50 (8%)	3/48 (6%)	4/48 (8%)	2/49 (4%)
Adjusted Rates (b)	9.9%	7.9%	13.7%	7.6%
Terminal Rates (c)	3/38 (8%)	3/38 (8%)	3/27 (11%)	1/23 (4%)
Life Table Tests (d)	P=0.534N	P=0.498N	P=0.484	P=0.522N
Incidental Tumor Tests (d)	P=0.363N	P=0.500N	P=0.575	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.303N			
Fisher Exact Test		P=0.523N	P=0.619	P=0.349N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	5/48 (10%)	4/48 (8%)	2/49 (4%)
Adjusted Rates (b)	9.9%	13.2%	13.7%	7.6%
Terminal Rates (c)	3/38 (8%)	5/38 (13%)	3/27 (11%)	1/23 (4%)
Life Table Tests (d)	P=0.462N	P=0.502	P=0.484	P=0.522N
Incidental Tumor Tests (d)	P=0.307N	P=0.500	P=0.575	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.226N			
Fisher Exact Test		P=0.474	P=0.619	P=0.349N
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	4/50 (8%)	0/49 (0%)	2/47 (4%)	0/47 (0%)
Adjusted Rates (b)	10.5%	0.0%	5.9%	0.0%
Terminal Rates (c)	4/38 (11%)	0/38 (0%)	1/28 (4%)	0/23 (0%)
Life Table Tests (d)	P=0.118N	P=0.063N	P=0.463N	P=0.143N
Incidental Tumor Tests (d)	P=0.106N	P=0.063N	P=0.459N	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.069N			
Fisher Exact Test		P=0.061N	P=0.369N	P=0.066N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Pancreatic Islets: Islet Cell Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	0/49 (0%)	3/47 (6%)	0/47 (0%)
Adjusted Rates (b)	10.5%	0.0%	9.4%	0.0%
Terminal Rates (c)	4/38 (11%)	0/38 (0%)	2/28 (7%)	0/23 (0%)
Life Table Tests (d)	P=0.169N	P=0.063N	P=0.644N	P=0.143N
Incidental Tumor Tests (d)	P=0.155N	P=0.063N	P=0.640N	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.096N			
Fisher Exact Test		P=0.061N	P=0.535N	P=0.066N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	7.9%	9.3%	3.6%	8.7%
Terminal Rates (c)	3/38 (8%)	1/38 (3%)	1/28 (4%)	2/23 (9%)
Life Table Tests (d)	P=0.476N	P=0.501	P=0.419N	P=0.644
Incidental Tumor Tests (d)	P=0.304N	P=0.455	P=0.419N	P=0.644
Cochran-Armitage Trend Test (d)	P=0.292N			
Fisher Exact Test		P=0.500	P=0.309N	P=0.500N
Mammary Gland: Fibroadenoma or Adenoma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.9%	9.3%	6.3%	8.7%
Terminal Rates (c)	3/38 (8%)	1/38 (3%)	1/28 (4%)	2/23 (9%)
Life Table Tests (d)	P=0.507N	P=0.501	P=0.626N	P=0.644
Incidental Tumor Tests (d)	P=0.268N	P=0.455	P=0.533N	P=0.644
Cochran-Armitage Trend Test (d)	P=0.319N			
Fisher Exact Test		P=0.500	P=0.500N	P=0.500N
Preputial Gland: Adenoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.6%	2.6%	9.8%	7.6%
Terminal Rates (c)	1/38 (3%)	1/38 (3%)	2/28 (7%)	1/23 (4%)
Life Table Tests (d)	P=0.176	P=0.762	P=0.215	P=0.355
Incidental Tumor Tests (d)	P=0.342	P=0.762	P=0.296	P=0.522
Cochran-Armitage Trend Test (d)	P=0.324			
Fisher Exact Test		P=0.753	P=0.309	P=0.500
Preputial Gland: Adenoma or Carcinoma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	7.9%	2.6%	9.8%	11.8%
Terminal Rates (c)	3/38 (8%)	1/38 (3%)	2/28 (7%)	2/23 (9%)
Life Table Tests (d)	P=0.242	P=0.305N	P=0.526	P=0.438
Incidental Tumor Tests (d)	P=0.400	P=0.305N	P=0.614	P=0.562
Cochran-Armitage Trend Test (d)	P=0.456			
Fisher Exact Test		P=0.309N	P=0.661	P=0.661
Testis: Interstitial Cell Tumor				
Overall Rates (a)	45/50 (90%)	45/50 (90%)	44/50 (88%)	46/49 (94%)
Adjusted Rates (b)	93.7%	100.0%	97.8%	100.0%
Terminal Rates (c)	35/38 (92%)	38/38 (100%)	27/28 (96%)	23/23 (100%)
Life Table Tests (d)	P<0.001	P=0.578	P=0.052	P=0.003
Incidental Tumor Tests (d)	P=0.171	P=0.649	P=0.639N	P=0.205
Cochran-Armitage Trend Test (d)	P=0.310			
Fisher Exact Test		P=0.630N	P=0.500N	P=0.369
Testis: Mesothelioma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	0.0%	0.0%	7.9%	0.0%
Terminal Rates (c)	0/38 (0%)	0/38 (0%)	0/28 (0%)	0/23 (0%)
Life Table Tests (d)	P=0.499	(e)	P=0.100	(e)
Incidental Tumor Tests (d)	P=0.504N	(e)	P=0.284	(e)
Cochran-Armitage Trend Test (d)	P=0.534			
Fisher Exact Test		(e)	P=0.121	(e)

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
All Sites: Mesothelioma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	2.2%	2.5%	13.3%	0.0%
Terminal Rates (c)	0/38 (0%)	0/38 (0%)	1/28 (4%)	0/23 (0%)
Life Table Tests (d)	P=0.551N	P=0.752N	P=0.084	P=0.504N
Incidental Tumor Tests (d)	P=0.204N	P=0.729	P=0.226	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.474N			
Fisher Exact Test		P=0.753	P=0.102	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is presented because no tumors were observed in the vehicle control, 150, and 600 mg/kg groups.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	9/50 (18%)	13/50 (26%)	12/49 (24%)	18/50 (36%)
Adjusted Rates (b)	20.1%	32.0%	29.5%	49.5%
Terminal Rates (c)	3/36 (8%)	8/35 (23%)	6/33 (18%)	7/25 (28%)
Life Table Tests (d)	P=0.005	P=0.215	P=0.259	P=0.008
Incidental Tumor Tests (d)	P=0.063	P=0.196	P=0.284	P=0.051
Cochran-Armitage Trend Test (d)	P=0.032			
Fisher Exact Test		P=0.235	P=0.294	P=0.035
Pituitary: Adenoma				
Overall Rates (a)	9/50 (18%)	14/50 (28%)	14/46 (30%)	13/50 (26%)
Adjusted Rates (b)	22.9%	37.4%	37.3%	37.1%
Terminal Rates (c)	6/36 (17%)	12/35 (34%)	9/31 (29%)	6/25 (24%)
Life Table Tests (d)	P=0.062	P=0.151	P=0.109	P=0.073
Incidental Tumor Tests (d)	P=0.209	P=0.113	P=0.098	P=0.232
Cochran-Armitage Trend Test (d)	P=0.264			
Fisher Exact Test		P=0.171	P=0.118	P=0.235
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	11/50 (22%)	16/50 (32%)	14/46 (30%)	13/50 (26%)
Adjusted Rates (b)	27.2%	42.9%	37.3%	37.1%
Terminal Rates (c)	7/36 (19%)	14/35 (40%)	9/31 (29%)	6/25 (24%)
Life Table Tests (d)	P=0.148	P=0.161	P=0.218	P=0.151
Incidental Tumor Tests (d)	P=0.386	P=0.111	P=0.207	P=0.403
Cochran-Armitage Trend Test (d)	P=0.467			
Fisher Exact Test		P=0.184	P=0.239	P=0.408
Adrenal: Pheochromocytoma				
Overall Rates (a)	1/50 (2%)	5/50 (10%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	2.6%	12.4%	8.3%	7.6%
Terminal Rates (c)	0/36 (0%)	3/35 (9%)	2/33 (6%)	1/25 (4%)
Life Table Tests (d)	P=0.458	P=0.101	P=0.274	P=0.374
Incidental Tumor Tests (d)	P=0.454N	P=0.163	P=0.310	P=0.510
Cochran-Armitage Trend Test (d)	P=0.563N			
Fisher Exact Test		P=0.102	P=0.301	P=0.500
Mammary Gland: Fibroadenoma				
Overall Rates (a)	11/50 (22%)	11/50 (22%)	12/49 (24%)	3/50 (6%)
Adjusted Rates (b)	29.3%	30.2%	32.6%	10.8%
Terminal Rates (c)	10/36 (28%)	10/35 (29%)	9/33 (27%)	2/25 (8%)
Life Table Tests (d)	P=0.095N	P=0.565	P=0.412	P=0.087N
Incidental Tumor Tests (d)	P=0.054N	P=0.592	P=0.382	P=0.059N
Cochran-Armitage Trend Test (d)	P=0.020N			
Fisher Exact Test		P=0.595N	P=0.478	P=0.021N
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	6/50 (12%)	5/50 (10%)	10/49 (20%)	7/50 (14%)
Adjusted Rates (b)	15.9%	14.3%	26.1%	21.4%
Terminal Rates (c)	5/36 (14%)	5/35 (14%)	6/33 (18%)	3/25 (12%)
Life Table Tests (d)	P=0.138	P=0.524N	P=0.168	P=0.281
Incidental Tumor Tests (d)	P=0.271	P=0.548N	P=0.214	P=0.473
Cochran-Armitage Trend Test (d)	P=0.338			
Fisher Exact Test		P=0.500N	P=0.194	P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	150 mg/kg	300 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.3%	2.4%	2.3%
Terminal Rates (c)	3/41 (7%)	0/36 (0%)	0/39 (0%)
Life Table Tests (d)	P=0.212N	P=0.342N	P=0.318N
Incidental Tumor Tests (d)	P=0.136N	P=0.228N	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test		P=0.309N	P=0.309N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.3%	5.1%	2.3%
Terminal Rates (c)	3/41 (7%)	1/36 (3%)	0/39 (0%)
Life Table Tests (d)	P=0.235N	P=0.547N	P=0.318N
Incidental Tumor Tests (d)	P=0.163N	P=0.436N	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test		P=0.500N	P=0.309N
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.3%	7.2%	2.3%
Terminal Rates (c)	3/41 (7%)	1/36 (3%)	0/39 (0%)
Life Table Tests (d)	P=0.252N	P=0.622	P=0.318N
Incidental Tumor Tests (d)	P=0.228N	P=0.611N	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test		P=0.661	P=0.309N
Integumentary System: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	7.3%	9.8%	2.3%
Terminal Rates (c)	3/41 (7%)	2/36 (6%)	0/39 (0%)
Life Table Tests (d)	P=0.268N	P=0.452	P=0.318N
Incidental Tumor Tests (d)	P=0.248N	P=0.543	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test		P=0.500	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	11.9%	15.6%	15.4%
Terminal Rates (c)	4/41 (10%)	4/36 (11%)	6/39 (15%)
Life Table Tests (d)	P=0.410	P=0.429	P=0.470
Incidental Tumor Tests (d)	P=0.482	P=0.596N	P=0.523
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test		P=0.500	P=0.500
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	4.9%	7.7%	2.6%
Terminal Rates (c)	2/41 (5%)	2/36 (6%)	1/39 (3%)
Life Table Tests (d)	P=0.416N	P=0.457	P=0.517N
Incidental Tumor Tests (d)	P=0.490N	P=0.453	P=0.517N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.500	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	14.2%	20.1%	17.9%
Terminal Rates (c)	5/41 (12%)	5/36 (14%)	7/39 (18%)
Life Table Tests (d)	P=0.413	P=0.319	P=0.466
Incidental Tumor Tests (d)	P=0.435	P=0.518	P=0.515
Cochran-Armitage Trend Test (d)	P=0.443		
Fisher Exact Test		P=0.387	P=0.500

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	6.7%	11.5%	4.7%
Terminal Rates (c)	1/41 (2%)	0/36 (0%)	1/39 (3%)
Life Table Tests (d)	P=0.430N	P=0.342	P=0.507N
Incidental Tumor Tests (d)	P=0.538N	P=0.617N	P=0.691N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test		P=0.357	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	7.7%	4.5%
Terminal Rates (c)	0/41 (0%)	2/36 (6%)	0/39 (0%)
Life Table Tests (d)	P=0.206	P=0.109	P=0.248
Incidental Tumor Tests (d)	P=0.276	P=0.172	P=0.451
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test		P=0.121	P=0.247
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	14.6%	20.5%	9.7%
Terminal Rates (c)	6/41 (15%)	6/36 (17%)	3/39 (8%)
Life Table Tests (d)	P=0.353N	P=0.303	P=0.396N
Incidental Tumor Tests (d)	P=0.412N	P=0.366	P=0.485N
Cochran-Armitage Trend Test (d)	P=0.322N		
Fisher Exact Test		P=0.387	P=0.371N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	12/50 (24%)
Adjusted Rates (b)	13.5%	13.4%	27.1%
Terminal Rates (c)	3/41 (7%)	1/36 (3%)	7/39 (18%)
Life Table Tests (d)	P=0.076	P=0.586	P=0.100
Incidental Tumor Tests (d)	P=0.032	P=0.425N	P=0.101
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test		P=0.620N	P=0.096
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (b)	24.9%	29.3%	33.2%
Terminal Rates (c)	8/41 (20%)	6/36 (17%)	9/39 (23%)
Life Table Tests (d)	P=0.213	P=0.338	P=0.237
Incidental Tumor Tests (d)	P=0.118	P=0.549	P=0.212
Cochran-Armitage Trend Test (d)	P=0.212		
Fisher Exact Test		P=0.408	P=0.247

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

	Vehicle Control	300 mg/kg	600 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	2/46 (4%)	3/50 (6%)
Adjusted Rates (b)	4.9%	5.1%	8.8%
Terminal Rates (c)	2/41 (5%)	2/39 (5%)	3/34 (9%)
Life Table Tests (d)	P=0.328	P=0.677	P=0.415
Incidental Tumor Tests (d)	P=0.328	P=0.677	P=0.415
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test		P=0.659	P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/46 (7%)	4/50 (8%)
Adjusted Rates (b)	9.0%	7.7%	11.8%
Terminal Rates (c)	2/41 (5%)	3/39 (8%)	4/34 (12%)
Life Table Tests (d)	P=0.473	P=0.529N	P=0.536
Incidental Tumor Tests (d)	P=0.464	P=0.613N	P=0.537
Cochran-Armitage Trend Test (d)	P=0.575		
Fisher Exact Test		P=0.547N	P=0.643
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	8/47 (17%)	6/50 (12%)
Adjusted Rates (b)	20.1%	18.1%	15.7%
Terminal Rates (c)	6/41 (15%)	4/39 (10%)	3/34 (9%)
Life Table Tests (d)	P=0.384N	P=0.548N	P=0.435N
Incidental Tumor Tests (d)	P=0.294N	P=0.435N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.246N		
Fisher Exact Test		P=0.557N	P=0.288N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	9/50 (18%)	9/47 (19%)	7/50 (14%)
Adjusted Rates (b)	20.1%	19.9%	17.7%
Terminal Rates (c)	6/41 (15%)	4/39 (10%)	3/34 (9%)
Life Table Tests (d)	P=0.498N	P=0.548	P=0.547N
Incidental Tumor Tests (d)	P=0.337N	P=0.490N	P=0.449N
Cochran-Armitage Trend Test (d)	P=0.345N		
Fisher Exact Test		P=0.545	P=0.393N
Circulatory System: Hemangioma			
Overall Rates (a)	3/50 (6%)	0/47 (0%)	1/50 (2%)
Adjusted Rates (b)	7.3%	0.0%	2.9%
Terminal Rates (c)	3/41 (7%)	0/39 (0%)	1/34 (3%)
Life Table Tests (d)	P=0.216N	P=0.130N	P=0.374N
Incidental Tumor Tests (d)	P=0.216N	P=0.130N	P=0.374N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test		P=0.133N	P=0.309N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	2/47 (4%)	0/49 (0%)
Adjusted Rates (b)	9.8%	5.1%	0.0%
Terminal Rates (c)	4/41 (10%)	2/39 (5%)	0/34 (0%)
Life Table Tests (d)	P=0.053N	P=0.360N	P=0.089N
Incidental Tumor Tests (d)	P=0.053N	P=0.360N	P=0.089N
Cochran-Armitage Trend Test (d)	P=0.040N		
Fisher Exact Test		P=0.369N	P=0.061N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	2/47 (4%)	2/49 (4%)
Adjusted Rates (b)	7.3%	4.9%	5.9%
Terminal Rates (c)	3/41 (7%)	1/39 (3%)	2/34 (6%)
Life Table Tests (d)	P=0.486N	P=0.522N	P=0.585N
Incidental Tumor Tests (d)	P=0.456N	P=0.518N	P=0.585N
Cochran-Armitage Trend Test (d)	P=0.416N		
Fisher Exact Test		P=0.530N	P=0.510N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	4/47 (9%)	2/49 (4%)
Adjusted Rates (b)	17.1%	9.9%	5.9%
Terminal Rates (c)	7/41 (17%)	3/39 (8%)	2/34 (6%)
Life Table Tests (d)	P=0.091N	P=0.291N	P=0.131N
Incidental Tumor Tests (d)	P=0.083N	P=0.289N	P=0.131N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test		P=0.299N	P=0.085N
Pituitary: Chromophobe Adenoma			
Overall Rates (a)	10/49 (20%)	7/46 (15%)	6/41 (15%)
Adjusted Rates (b)	23.7%	17.9%	20.7%
Terminal Rates (c)	8/40 (20%)	6/38 (16%)	6/29 (21%)
Life Table Tests (d)	P=0.360N	P=0.343N	P=0.436N
Incidental Tumor Tests (d)	P=0.338N	P=0.327N	P=0.414N
Cochran-Armitage Trend Test (d)	P=0.272N		
Fisher Exact Test		P=0.349N	P=0.333N
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	4/45 (9%)	0/47 (0%)	1/45 (2%)
Adjusted Rates (b)	10.8%	0.0%	3.1%
Terminal Rates (c)	4/37 (11%)	0/39 (0%)	1/32 (3%)
Life Table Tests (d)	P=0.098N	P=0.056N	P=0.225N
Incidental Tumor Tests (d)	P=0.098N	P=0.056N	P=0.225N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test		P=0.053N	P=0.180N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence. A negative or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.	
Diallylphthalate	13/50
Tris(2-ethylhexyl)phosphate	2/50
Toluenediisocyanate	11/50
TOTAL	26/150 (17.3%)
SD (b)	11.72%
Range (c)	
High	13/50
Low	2/50
Overall Historical Incidence	
TOTAL	140/1,146 (12.2%)
SD (b)	7.59%
Range (c)	
High	13/50
Low	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.	
Diallylphthalate	15/50
Tris(2-ethylhexyl)phosphate	8/50
Toluenediisocyanate	21/50
TOTAL	44/150 (29.3%)
SD (b)	13.01%
Range (c)	
High	21/50
Low	8/50
Overall Historical Incidence	
TOTAL	185/1,147 (16.1%)
SD (b)	8.90%
Range (c)	
High	21/50
Low	1/49

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	0/50	0/50	0/50
Tris(2-ethylhexyl)phosphate	1/50	0/50	1/50
Toluenediisocyanate	1/50	0/50	1/50
TOTAL	2/150 (1.3%)	0/150 (0.0%)	2/150 (1.3%)
SD (b)	1.15%	0.00%	1.15%
Range (c)			
High	1/50	0/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	12/1,094 (1.1%)	9/1,094 (0.8%)	21/1,094 (1.9%)
SD (b)	1.72%	1.47%	2.65%
Range (c)			
High	3/50	3/50	5/50
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Toluenediisocyanate	5/49	6/49	11/49
Diallylphthalate	0/50	7/50	7/50
Tris(2-ethylhexyl)phosphate	7/50	9/50	15/50
TOTAL	12/149 (8.1%)	22/149 (14.8%)	33/149 (22.1%)
SD (b)	7.24%	2.95%	8.00%
Range (c)			
High	7/50	9/50	15/50
Low	0/50	6/49	7/50
Overall Historical Incidence			
TOTAL	133/1,084 (12.3%)	(d) 222/1,084 (20.5%)	340/1,084 (31.4%)
SD (b)	6.70%	7.90%	10.30%
Range (c)			
High	13/50	18/50	25/50
Low	0/50	4/50	5/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) One hepatoblastoma also was observed.

APPENDIX G

CHEMICAL CHARACTERIZATION OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

I. Identity and Purity Determinations of Dimethyl Morpholinophosphoramidate (DMMPA) Performed by the Analytical Chemistry Laboratory

A. Lot No. E112877 (Batch 01)

1. Physical Properties

a. Boiling Point:	Determined	Literature Values
	Boils with decomposition at 205° C (visual, Büchi apparatus at 768 torr)	108°-109° C at 3 mm Hg (Arbuzov et al., 1964)

b. Density:	Determined	Literature Values
	d_{22}^{25}: 1.22370 ± 0.00015	1.223 at 20° C (Coleman, 1977a)

c. Index of Refraction:	Determined	Literature Values
	n_D^{20}: 1.4537 ± 0.0002	n_D^{25}: 1.4530 (Coleman, 1977a)

d. Appearance: Clear, colorless, slightly viscous liquid

2. Spectral Data

a. Infrared	Determined	Literature Values
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 5	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield, Canada

b. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	95% ethanol	
Results:	There was no absorbance from 800 to 350 nm; no maxima in the ultraviolet region, but a gradual increase in absorbance toward the solvent cutoff	No literature reference found

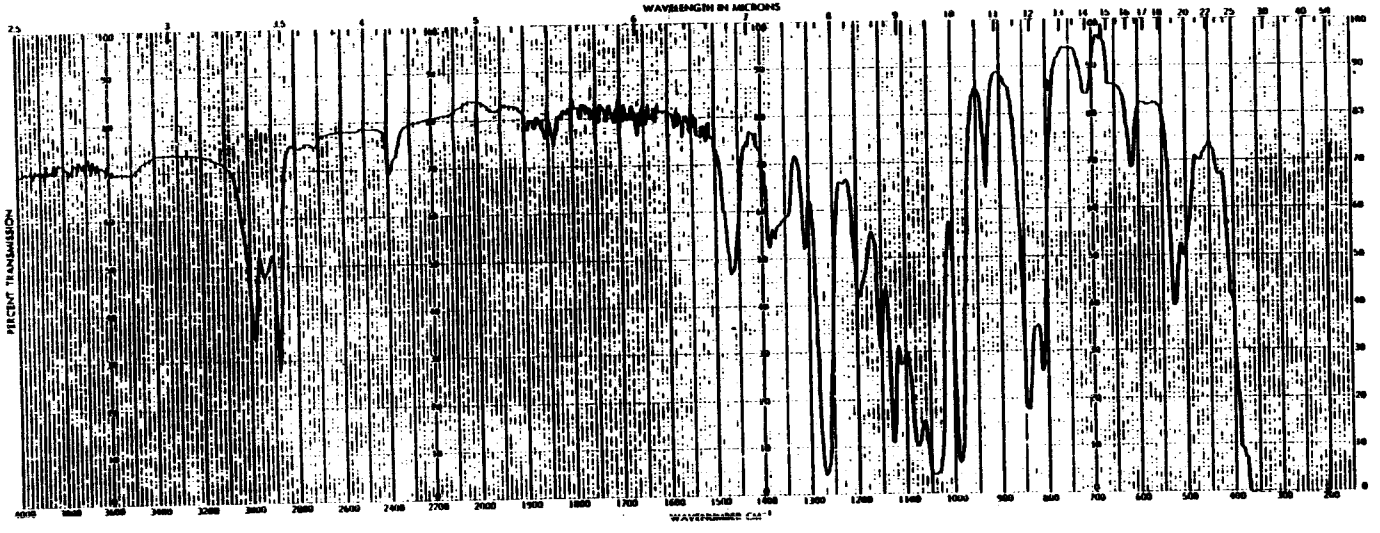


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. E112877, BATCH 01)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with internal tetramethylsilane standard	
Assignments:	See Figure 6	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield, Canada
Chemical Shift (δ):	a m, 2.95-3.30 ppm b m, 3.45-3.84 ppm c d, 3.68 ppm	
Coupling Constant:	J_{P-C} = 11 Hz	
Integration Ratios:	a 4.80 b, c } 9.21	

3. **Water Analysis (Karl Fischer):** 0.16% ± 0.01 (δ)%

4. **Elemental Analysis**

Element	C	H	N	P
Theory (T)	36.93	7.23	7.18	15.87
Determined (D)	36.52 36.67	7.22 7.13	7.40 7.32	15.54 15.61
Percent D/T	99.09	99.24	102.51	98.14

5. **Chromatographic Analyses**

a. **Thin-Layer Chromatography**

Plates: Analtech Silica gel G, 250 µ coating
Ref. standard: Trimethyl phosphate
Amount spotted: 90 µg and 300 µg (30 mg/ml chloroform)
Visualization: Iodine vapor

(1) **System 1:** Chloroform:methanol (90:10)

R_f: 0.76 (major), 0.64 (trace), 0.35 (trace), 0.05 (trace), origin (trace)

R_{st}: 0.98, 0.82, 0.45, 0.06, origin

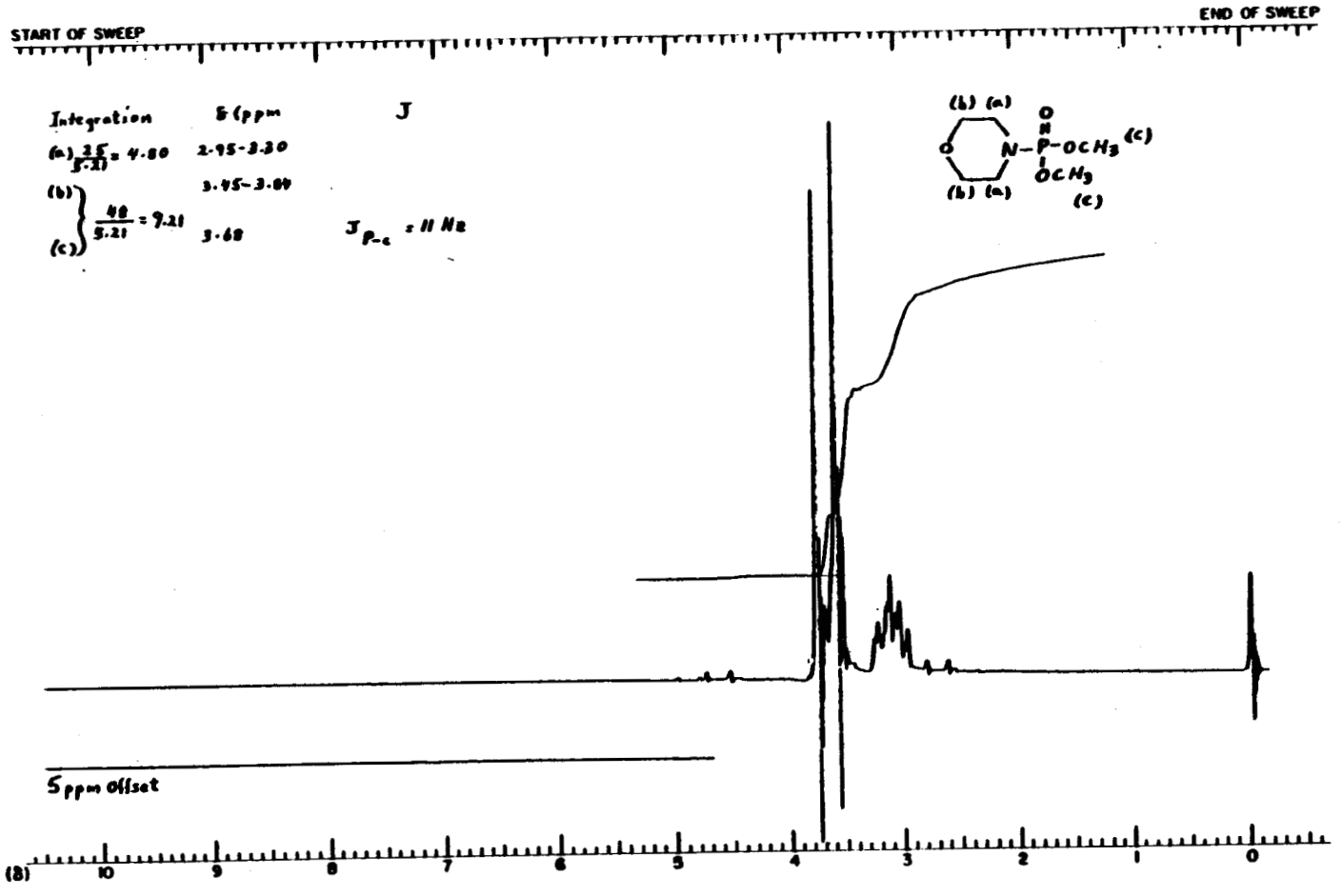


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. E112877, BATCH 01)

(2) System 2: Acetone:ethyl acetate (50:50)

R_f: 0.31 (major), 0.17 (trace), 0.05 (trace), origin (trace)

R_{st}: 0.66, 0.36, 0.11, origin

b. Gas Chromatography

(1) System 1

Instrument: Tracor MT-220
Detector: Flame ionization
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 190° C
Detector temperature: 235° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 50° C for 5 min, 50°-170° C at 10° C/min
Sample injected: 4 µl of a 20% solution in toluene, diluted to 1% and 0.5% in toluene to quantitate major peak and check for overloading

Results: Major peak and seven impurities. One impurity had an area 0.17% that of the major peak area; the remaining six impurities had a combined area less than 0.4% that of the major peak area

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	12.8	0.70	0.06
2	16.0	0.88	0.06
3	16.5	0.91	0.04
4	16.8	0.92	0.02
5	18.2	1.00	100
6	20.0	1.10	0.17
7	24.5	1.35	0.10
8	27.9	1.53	0.03

(2) System 2

Instrument: Tracor MT-220
Detector: Flame ionization
Column: Igepal CO 880 on 100/120 Chromosorb P (AW) DMCS, 1.8 m × 4 mm ID, glass
Inlet temperature: 195° C
Detector temperature: 235° C
Carrier gas: Nitrogen
Carrier flow rate: 80 ml/min
Oven temperature program: 165° C isothermal
Sample injected: 6 µl of a 20% solution in toluene, diluted to 1% and 0.5% in toluene to quantitate major peak and check for overloading

Results: Major peak and one impurity

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	7.1	1.00	100
2	15.3	2.15	0.06

(3) System 3: A sample of this lot was compared to a "very pure" standard of DMMPA received from the Defence Research Establishment of Suffield. The sample and standard were accurately weighed and diluted with toluene containing an internal standard of triethylphosphate and analyzed with the following gas chromatographic system:

Instrument: Tracor MT-220
Detector: Flame ionization
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 190° C
Detector temperature: 230° C
Carrier gas: Nitrogen
Carrier flow rate: 80 ml/min
Oven temperature program: 170° C isothermal
Sample injected: 4 µl

Results

	Area (percent of pure DMMPA standard)
Pure Standard DMMPA	100 ± 1
Analytical Sample DMMPA	99 ± 1

6. Conclusions: The results of the elemental analysis for carbon, hydrogen, nitrogen and phosphorus were in agreement with the theoretical values. Gas chromatography by one system indicated seven impurities, one of which had an area 0.17% that of the major peak area. The other six impurities had areas totaling less than 0.4% that of the major peak area. A second gas chromatography system indicated one impurity with an area 0.06% that of the major peak area. Thin-layer chromatography by one system indicated four trace impurities, by a second system, three trace impurities. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with the structure. A gas chromatographic quantitative comparison of the bulk material and a "very pure" standard indicated the purity of the bulk material to be 100% ± 1% experimental error of the analysis.

B. Lot No. E112877 (Batch 02)

1. Appearance:	Clear, colorless, slightly viscous liquid	
2. Spectral Data		
a. Infrared	Determined	Literature Values
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 7	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield, Canada, and the spectrum of lot no. E112877, batch 01
b. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	95% ethanol	
Results:	There was no absorbance from 800 to 350 nm at a concentration of 1% v/v; no maximum between 350 and 215 nm but a gradual increase in absorbance toward the solvent cutoff	No literature reference found. Spectrum consistent with DMMPA structure
c. Nuclear Magnetic Resonance		
	Determined	Literature Values
Instrument:	Varian EM360-A	
Solvent:	Deuterated chloroform with internal tetra-methylsilane standard	
Assignments:	See Figure 8	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield, Canada

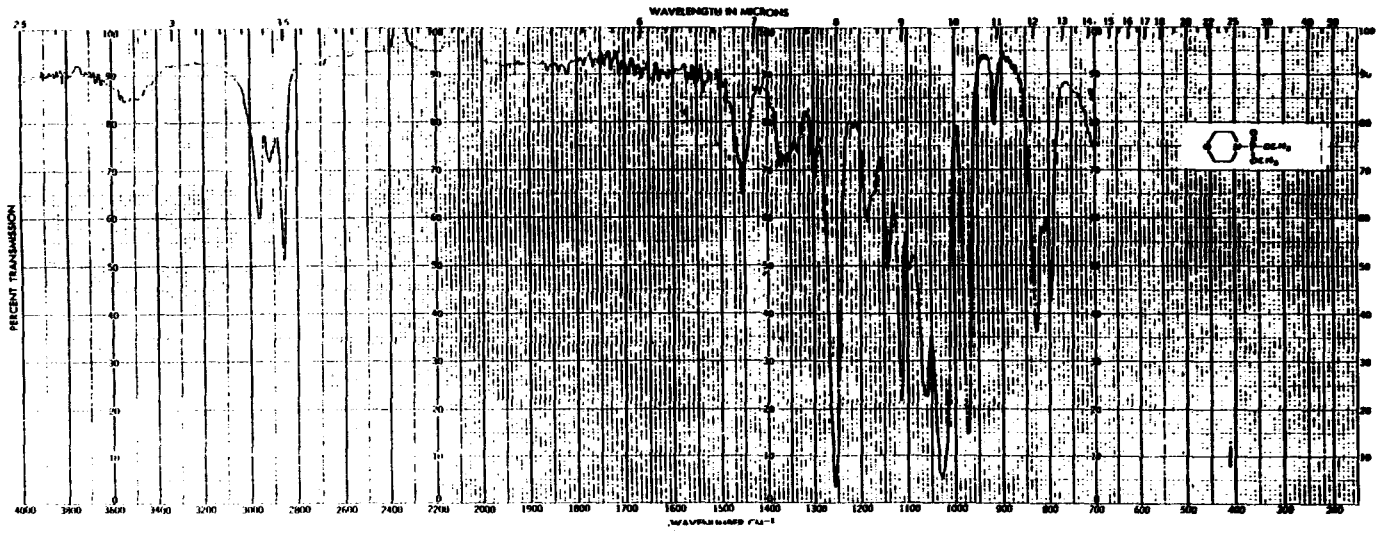


FIGURE 7. INFRARED ABSORPTION SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. E11287, BATCH 02)

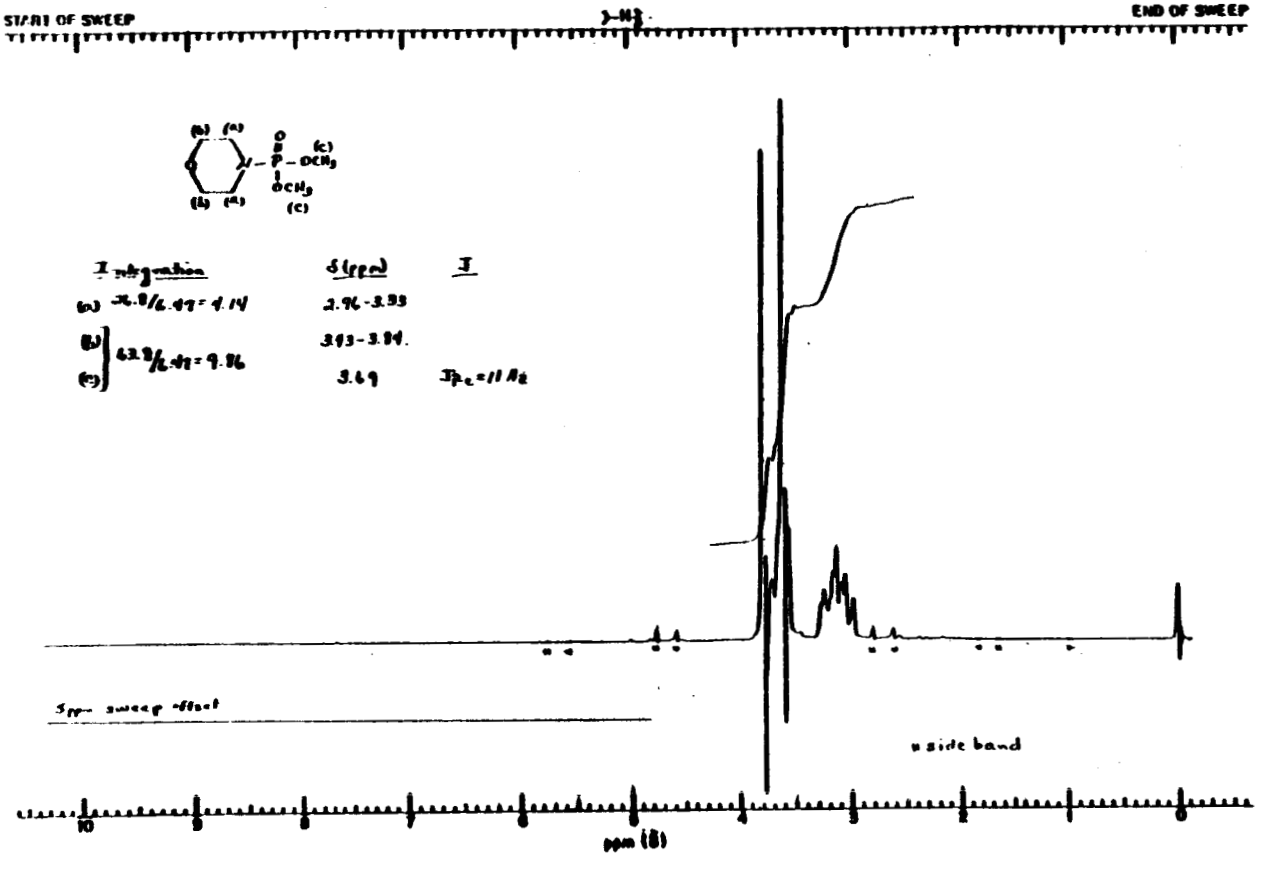


FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. E112877, BATCH 02)

Chemical Shift (δ):
a m, 2.96-3.33 ppm
b m, 3.43-3.84 ppm
c d, 3.69 ppm

Coupling Constant: $J_{P\text{-}c}$ = 11 Hz

Integration Ratios:
a 4.14
b, c 9.86

3. Water Analysis (Karl Fischer): 0.086% ± 0.006 (δ)%

4. Elemental Analysis

Element	C	H	N	P
Theory (T)	36.93	7.23	7.18	15.87
Determined (D)	36.37	7.23	7.31	15.81
	36.46	7.24	7.28	15.67
Percent D/T	98.60	100.07	101.60	99.18

5. Chromatographic Analyses

a. Thin-Layer Chromatography

Plates: Silica Gel 60, F-254, 0.25 mm layer thickness
Ref. standard: Triphenyl phosphate, 10 µg (1 µl of a 10 µg/µl solution in chloroform
Amount spotted: 10, 100, and 300 µg (1, 10, and 30 µl of a 10 µg/µl) solution in chloroform
Visualization: Ultraviolet light (254 nm) for reference and iodine vapor for sample and reference

(1) **System 1:** Chloroform:methanol (90:10)

R_f: 0.55 (major), 0.46 (minor), 0.35 (trace), 0.26 (slight trace), 0.14 (minor), 0.06 (slight trace), origin (trace), 0.78 (reference)

R_{st}: 0.70, 0.59, 0.45, 0.33, 0.18, 0.08, origin

(2) **System 2:** Acetone (100%)

R_f: 0.42 (slight trace), 0.30 (major), 0.20 (minor), 0.14 (slight trace), 0.09 (slight trace), 0.02 (minor), origin (trace), 0.69 (reference)

R_{st}: 0.60, 0.44, 0.29, 0.20, 0.13, 0.03, origin

b. Gas Chromatography

(1) System 1

Instrument: Varian 3700
Detector: Flame ionization
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 190° C
Detector temperature: 240° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 50° C for 5 min, 50°-170° C at 10° C/min
Sample injected: 3 µl of a 20% solution in toluene, diluted to 1% and 0.5% in toluene to quantitate major peak and check for overloading

Results: Major peak and nine impurities. One impurity had an area 0.25% that of the major peak area; the remaining eight impurities had a combined area 0.32% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	12.0	0.62	0.10
2	15.7	0.82	0.01
3	17.0	0.88	0.07
4	17.6	0.92	0.01
5	18.2	0.95	0.01
6	18.7	0.97	0.01
7	19.2	1.00	100
8	22.6	1.18	0.25
9	28.3	1.47	0.10
10	31.9	1.66	0.01

(2) System 2

Instrument: Varian 3700
Detector: Flame ionization
Column: 3% Igepal CO 880 on 100/120 Chromosorb P (AW) DMCS, 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 240° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 165° C, isothermal
Sample injected: 3 µl of a 20% DMMPA solution in toluene, diluted to 1% and 0.5% in toluene to quantitate major peak and check for overloading

Results: Major peak and one impurity

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	4.2	0.49	0.01
2	8.5	1.00	100

6. Conclusions: The result of the elemental analysis for carbon was slightly low, whereas the results for hydrogen, nitrogen, and phosphorus were in agreement with the theoretical values. Karl Fischer analysis indicated 0.086% ± 0.006% water. Thin layer chromatography by one system indicated a major spot and two minor, two trace, and two slight trace impurities. A second thin-layer chromatography system indicated a major spot and two minor, one trace, and three slight trace impurities. Gas chromatography by a 20% SP-2100/0.1% Carbowax 1500 column indicated a major peak and nine impurities, the largest of which had an area 0.25% of the major peak area. A second gas chromatography system by a 3% Igepal CO 880 column indicated a major peak and one impurity with an area 0.01% of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of DMMPA and with the spectra obtained for batch no. 1. Batch no. 1 and batch no. 2 are comparable in purity.

C. Lot No. D021381

1. **Appearance:** Clear, colorless, slightly viscous liquid

2. **Spectral Data**

a. Infrared	Determined	Literature Values
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 9	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield

b. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 219	
Solvent:	95% ethanol	
Results:	No absorbance between 800 nm and 350 nm at a concentration of 1% (v/v). No maximum between 350 and 215 nm, but a gradual increase in absorbance toward 215 nm at a concentration of 1% (v/v)	No literature reference found; spectrum consistent with structure

c. Nuclear Magnetic Resonance

	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with internal tetramethylsilane	
Assignments:	See Figure 10	No literature reference found; consistent with spectrum provided by Defence Research Establishment, Suffield

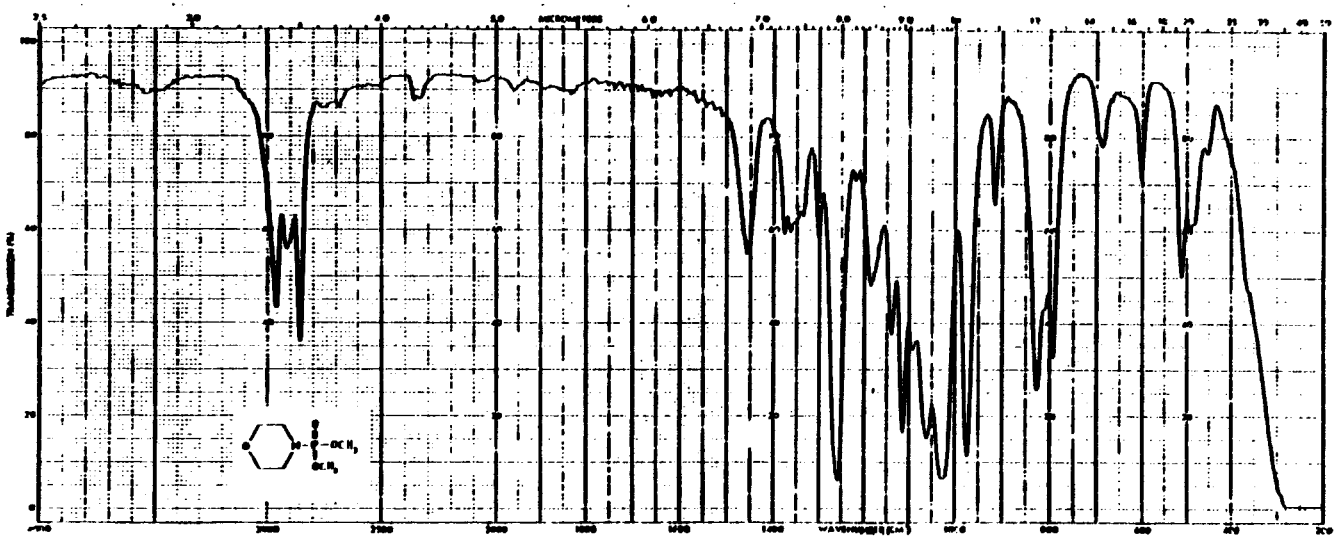


FIGURE 9. INFRARED ABSORPTION SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. D021381)

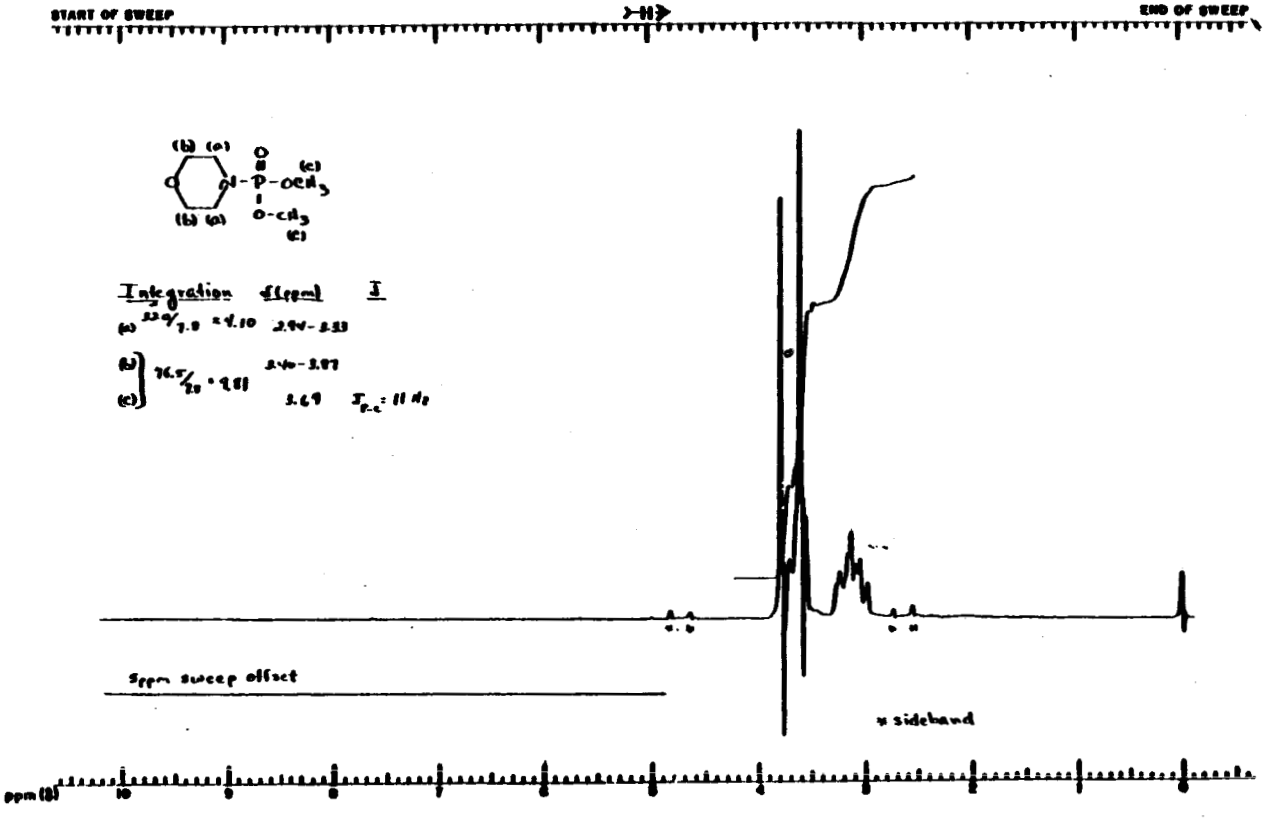


FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (LOT NO. D021381)

Chemical Shift (δ):
a m, 2.94-3.33 ppm
b m, 3.40-3.87 ppm
c d, 3.69 ppm

Coupling Constant: J_{P-C} = 11 Hz

Integration Ratios:
a 4.10
b, c } 9.81

3. Water Analysis (Karl Fischer): 0.10% ± 0.01 (δ)%

4. Elemental Analysis

Element	C	H	N	P
Theory (T)	36.93	7.23	7.18	15.87
Determined (D)	36.78 37.02	7.26 7.35	7.74 7.61	15.85 15.65
Percent D/T	99.92	101.04	106.89	99.24

5. Chromatographic Analyses

a. Thin-Layer Chromatography

Plates: Silica gel 60, F-254, 0.25 mm layer thickness
Ref. standard: Triphenyl phosphate (1 µl of a 10 µg/µl solution in chloroform)
Amount spotted: 10, 100, and 300 µg (1, 10, 30 µl of a 10 µg/µl solution in chloroform)
Visualization: Ultraviolet light (254 nm) for reference and iodine vapor for sample and reference

(1) System 1: Chloroform:methanol (90:10)

R_f: 0.52 (major), 0.44 (trace), 0.32 (trace), 0.25 (slight trace), 0.13 (minor), 0.07 (slight trace), 0.01 (trace), 0.75 (reference)

R_{st}: 0.69, 0.59, 0.43, 0.33, 0.17, 0.09, 0.01

(2) System 2: Acetone (100%)

R_f: 0.30 (major), 0.19 (trace), 0.14 (slight trace), 0.08 (slight trace), 0.02 (minor), origin (trace), 0.72 (reference)

R_{st}: 0.42, 0.26 , 0.19, 0.11, 0.03, origin

b. Gas Chromatography

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 240° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

(1) System 1

Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 min, 50°-170° C at 10° C/min
Samples injected: 3 µl-solutions of 20%, 1%, and 0.5% (v/v) in toluene to detect impurities, quantitate major peak and check for overloading

Results: Major peak and 10 impurities, 6 before and 4 after the major peak. One impurity had an area 0.26% that of the major peak area; the remaining nine impurities had a combined area 0.38% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	11.7	0.62	0.13
2	15.4	0.81	0.02
3	16.8	0.88	0.07
4	17.4	0.92	0.01
5	17.9	0.94	0.01
6	18.4	0.97	0.01
7	19.0	1.00	100
8	21.0	1.10	0.01
9	21.9	1.15	0.26
10	27.2	1.43	0.11
11	30.6	1.61	0.01

(2) System 2

Column: 3% Igepal CO 880 on 100/120 Chromosorb P (AW) DMCS, 1.8 m × 4 mm ID, glass
Oven temperature program: 165° C, isothermal
Samples injected: 3 µl-solutions of 20%, 1%, and 0.5% (v/v) in toluene to detect impurities, quantitate major peak and check for overloading

Results: Major peak and a group of unresolved impurities before the major peak with a combined area 0.03% that of the major peak area

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1 (group of unresolved peaks)	1.8-3.0	0.38-0.61	0.03
2	4.9	1.00	100

6. Conclusions: The result of the elemental analysis for nitrogen was slightly high, whereas the results for carbon, hydrogen, and phosphorus were in agreement with the theoretical values and with those obtained for Lot No. E112877. Karl Fischer analysis indicated 0.10% ± 0.01 (δ)% water. Thin-layer chromatography by one system indicated a major spot and one minor, three trace, and two slight trace impurities and by a second system, a major spot and one minor, two trace, and two slight trace impurities. (Nearly identical profiles were obtained when thin-layer chromatography by the same systems was performed on a sample of lot no. E112877 which had been stored at MRI.) Gas chromatography (20% SP-2100/0.1% Carbowax 1500 column) indicated a major peak and 10 impurities, the largest of which had an area 0.26% that of the major peak area, and the remainder of which had a combined area 0.38% that of the major peak area. A second gas chromatography system (3% Igepal CO 880 column) indicated a major peak and one group of unresolved impurities with an area 0.03% that of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure and with the spectra obtained for lot no. E112877.

II. Test Chemical Stability Study of Lot No. E112877 Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Samples were stored for 2 weeks in glass containers with Teflon®-lined lids at −20°, +5°, +25°, and +60° C.

B. Analytical Method: Gas chromatography (triethyl phosphate as internal standard)

Instrument: Tracor MT-220
Detector: Flame ionization
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm, ID, glass
Inlet temperature: 190° C
Detector temperature: 230° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 170° C, isothermal
Sample injected: 4 µl

C. Results

Storage Temperature (degrees centigrade)	Area (percent of −20° C sample average)
− 20	100 ± 4
+ 5	105 ± 4
+ 25	103 ± 4
+ 60	99 ± 4

D. Conclusion: DMMPA is stable for 2 weeks at temperatures up to 60° C within the limits of error of this analysis. However, the presence of yellowish discoloration in the 60° C sample indicated that some decomposition had occurred which was not measurable by the above analytical method.

III. Test Chemical Stability Study Performed by the Testing Laboratory

A. Storage Conditions: The chemical was stored at 4° C.

B. Purity and Identity Analysis

1. Purity Analysis by Gas Chromatography

Instrument: Hewlett Packard 5880 with 7672 Autosampler
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, silanized glass
Detector temperature: 240° C
Injector temperature: 190° C
Oven temperature program: 50° C for 3 min; 50°-170° C at 10° C/min; 170° C for 23 min
Carrier gas: Nitrogen
Carrier flow rate: 40 ml/min
Sample size: 1 µl each of 0.5%, 1.0%, and 20% DMMPA dissolved in toluene

2. Identity: The infrared absorption spectra of the sample was obtained as potassium bromide disks using a Perkin-Elmer 398.

C. Results

1. Purity

		Percent Purity	
Date	Lot No.	Bulk	Reference
12/19/78	E112877		99.399
12/22/78			99.555
			100.86
09/26/79		99.3	98.3
04/17/80			
08/11/80			
12/16/80		99.2	99.1
04/07/81		99.6	99.2
08/12/81		99.3	99.3
04/14/81	D0213/81	--	99.7
12/15/81		99.8	99.7
04/27/81		99.6	99.6
08/19/82		99.5	99.8

2. Identity: All bulk and reference IR spectra were essentially identical.

D. Conclusion: No notable degradation was observed throughout the studies.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX H. PREPARATION AND CHARACTERIZATION

I. Sample Preparation and Storage: Dimethyl morpholinophosphoramidate (9.78 g) was diluted to 100 ml with corn oil. The flask was manually shaken for 30 seconds and placed in an ultrasonic bath for 5 minutes. This solution was stored for 7 days at room temperature; no attempt was made to protect the solution from light. Samples (in duplicate) were removed for analysis at zero time and after 3, 5, and 7 days storage.

II. Sample Extraction and Analysis: Samples of the stock solution were transferred to septum vials, weighed (1.63 g), and diluted with methanol containing an internal standard (20 ml; 0.6% triethylphosphate in methanol). The vial was sealed, agitated on a vortex mixer (1 min), and placed in an ultrasonic bath (2 min). Aliquots for analysis were removed from the top methanol layer with a microliter syringe and analyzed by the gas chromatographic system described below.

A. Instrument: Bendix 2500 with Hewlett Packard 3380A integrator
B. Column: 3% OV-1 on 80/100 mesh Supelcoport, 1.8 m × 2 mm ID, glass
C. Detection: Flame ionization
D. Temperatures:
Inlet, 160° C
Oven, 90° C, isothermal
Detector, 225° C
E. Carrier gas: Nitrogen
F. Flow rate: 50 ml/min
G. Volume injected: 5 µl
H. Retention times:
Test chemical, 9.0 min
Reference standard, 2.5 min

III. Quality Control Protocols: Each analysis was performed in duplicate. Recovery studies were performed in duplicate both at the beginning and end of the 7-day period. Linearity studies were done at three concentrations: 6.5%, 13.1%, 21.8%; the least-squares plot linearity correlation coefficient was 0.99944 for the test chemical and 0.99996 for the internal standard.

IV. Results

Day	Theoretical Percent (w/v) Chemical/Vehicle	Determined Percent (w/v) Chemical/Vehicle (a)
0	9.78 ± <0.01	(b) 9.78 ± 0.13
3	9.78 ± <0.01	9.89 ± 0.14
5	9.78 ± <0.01	9.82 ± 0.13
7	9.78 ± <0.01	9.66 ± 0.13

(a) Corrected for a spike recovery yield of 92.1% ± 1.2%
(b) Mean ± standard deviation

V. Conclusion: Dimethyl morpholinophosphoramidate mixed with corn oil at a concentration of 10% (100 mg/ml) is stable, within the limits of error of this study, when stored at 25° C for 7 days.

APPENDIX I

ANALYSIS OF DOSE MIXTURES: METHODS

APPENDIX I. ANALYSIS: METHODS

I. Testing Laboratory

Procedure: Dimethyl morpholinophosphoramidate (DMMPA) was extracted from corn oil into methanol containing a fixed amount of triethylphosphate (TEP) per milliliter of extractant. TEP serves as the internal standard for gas chromatographic quantification of DMMPA.

A. Before June 1981: Five milliliters of internal standard extractant was added to each serum bottle, and the bottle was stoppered and sonicated for 5 minutes. It was then centrifuged at 1,000 rpm for 10 minutes, and aliquots of the methanol extract were prepared for gas chromatographic analysis.

B. After June 1981: SMI pipettes were used to transfer in duplicate 1.0-ml aliquots of each sample (45.0 mg/ml and 90.1 mg/ml) into 50-ml centrifuge tubes. In the case of the 180.2 mg/ml sample aliquot, 500 µl in duplicate was followed by 500 µl of corn oil.

1. **Instrument:** HP 5880A with 7672 ALS
2. **Column:** 10% Carbowax 20M TPA on Chromosorb W (AW), 1.8 m × 2 mm ID, glass
3. **Detector:** Flame ionization
4. **Carrier gas:** Nitrogen
5. **Flow rate:** 40 ml/min
6. **Temperatures**
   Oven: 170° C, isothermal (before 9/29/80); 170°-220° C at 25° C/min (after 9/29/80)
   Inlet: 175° C
   Detector: 225° C
7. **Retention times at 170° C isothermal**
   TEP: 1.7 min
   DMMPA: 8.5 min

II. Analytical Chemistry Laboratory

Procedure: Immediately before being sampled for analysis, the referee corn oil sample and the control corn oil were allowed to equilibrate to room temperature and were homogenized by mixing on a vortex mixer.

A. Preparation of Standard Spiked Corn Oil: Two standard solutions of DMMPA in methanol were prepared independently. These solutions were further diluted with methanol to concentrations bracketing the concentration of the corn oil sample. Aliquots (10-20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of control corn oil to make spiked corn oil standards. One 35-ml septum vial containing 2 g of control corn oil was treated with 10-20 ml of methanol for use as a blank. The vials were sealed with Teflon®-lined septa, and the spiked corn oil and the corn oil blank were used in the analysis procedure described below.

B. Preparation of Referee Sample: Three portions (~2 g each) of the referee corn oil sample were transferred to individually tared 35-ml septum vials and weighed to the nearest 0.001 g. Methanol (10-20 ml) was pipetted into each vial; the vials were sealed and the samples analyzed immediately by the following procedure.

C. Analysis: Vials containing the samples, standards, and the blank were agitated for 10 seconds on a vortex mixer and then shaken for 15-20 minutes at maximum stroke on a Burrell Model 75 Wrist-Action® shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of each methanol layer was combined with 4 ml of internal standard solution (TEP in methanol, 3-12 mg/ml) and diluted to 25-100 ml with methanol. The solutions were thoroughly mixed, and the DMMPA content of each solution was determined by the gas chromatographic system described below.

1. **Instrument:** Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
2. **Column:** 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 4 mm ID, glass, silanized
3. **Detection:** Flame ionization
4. **Detector temperature:** 250°C
5. **Inlet temperature:** 200°C
6. **Oven temperature:** 160°C isothermal
7. **Carrier gas:** Nitrogen
8. **Flow rate:** 30 ml/min
9. **Volume of solution injected:** 3 µl
10. **Retention times**
    DMMPA: 6.8-8.8 min
    TEP internal standard: 2.5-3.2 min

D. Quality Assurance Measures: The referee corn oil sample was analyzed in triplicate, and the control corn oil sample was analyzed once. Individually spiked portions of control corn oil (six concentrations bracketing the specified dose range of the referee sample) were prepared from two independently weighed standards and were used for obtaining standard data. Triplicate injections of each standard and sample were introduced into the gas chromatograph in a randomized order. All determinations were related to an internal standard incorporated into the sample solutions.

Results were computed from the linear regression equation obtained by plotting the ratio of the peak area of each spiked corn oil sample to the peak area of the internal standard versus the amount of chemical in the respective spiked corn oil sample.

APPENDIX J

ANALYSES OF DOSE MIXTURES: DATA

TABLE J1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Date Mixed	Concentration (a) of DMMPA in Corn Oil for Target Concentration (mg/ml)		
	Target	Determined	Percent of Target
02/07/80	0	0	
	20	22.1	111
	40	37.1	92.8
	80	80.2	100.3
	120	121.4	101.2
	160	154.8	96.8

(a) The data presented are the average of the results of duplicate analyses.

TABLE J2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Date Mixed	Concentration (a) of DMMPA in Corn Oil for Target Concentration (mg/ml)				
	45 mg/ml	90.1 mg/ml		180.2 mg/ml	
		Mouse	Rat	Mouse	Rat
05/13/80	43.2	89.8	88.9	172.5	173.3
07/08/80	47.3	91.9	89.7	160.6	171.8
09/02/80	41.8	90.3		167.0	
10/28/80	44.2	95.3		186.0	
12/23/80	40.9	82.7		171.0	
02/17/81	47.4	96.8		(b) 207.0	
02/23/81				(c) 189.0	
04/14/81	47.1	94.2		(b) 221.0	
06/09/81	44.0	87.5		171.0	
08/04/81	45.7			180.0	
08/07/81				(c) 181.0	
09/29/81	44.3	90.0		178.0	
11/24/81	43.8	89.9		178.0	
01/19/82	42.1	87.7		170.0	
03/16/82	46.0	92.5		185.4	
05/11/82	44.7	88.8			
07/06/82	45.2	(b) 99.9			
08/31/82	43.2	91.6			
Mean (mg/ml)	44.4	91.3	91.1	180.6	181.5
Standard deviation	1.96	4.18	4.22	16.69	15.80
Coefficient of variation (percent)	4.4	4.6	4.6	9.2	8.7
Range (mg/ml)	40.9-47.4	82.7-99.9	82.7-99.9	160.6-221.0	160.6-221.0
Number of samples	16	15	15	13	13

(a) The data presented are the average of results of duplicate analyses.
(b) Differs from target value by more than 10%
(c) Remix. Not included in mean.

TABLE J3. REFEREE SAMPLE DATA IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Testing (a) Laboratory	Referee (b) Laboratory
07/08/80	45	47.3	43.9
02/17/81	90.1	96.8	90.4
08/04/81	180.2	180	180.8
05/11/82	45	44.7	44.3
10/26/82	90.1	92.3	87.8

(a) The data presented are the results of duplicate analyses.
(b) The data presented are the results of triplicate analyses.

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (6, 12, and 24 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus Sendai (18 mo)	MHV (mouse hepatitis virus) (male mice:12,18, and 24 mo; female mice:24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (12, 18, and 24 mo)	RCV (rat coronavirus) Sendai (6 mo)	

II. Results

Results are presented in Table K1.

TABLE K1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS	6	10/10	PVM
		1/7	RCV
	12	9/10	PVM
	18	10/10	PVM
	24	10/10	PVM
MICE	6	10/10	None positive
	12	10/10	None positive
	18	9/9	None positive
	24	(male) 2/5	MHV
		(female) 4/5	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX L

GENETIC TOXICOLOGY OF

DIMETHYL MORPHOLINOPHOSPHORAMIDATE

TABLE L1. MUTAGENICITY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	96 ± 5.8	147 ± 2.6	134 ± 12.6
	100	116 ± 10.7	149 ± 10.0	158 ± 5.8
	333	115 ± 8.3	153 ± 5.8	146 ± 10.7
	1,000	111 ± 6.9	141 ± 1.2	159 ± 5.6
	3,333	106 ± 6.6	133 ± 4.0	159 ± 7.9
	10,000	131 ± 9.5	157 ± 4.8	156 ± 10.7
TA1535	0	15 ± 1.5	7 ± 1.2	6 ± 0.9
	100	22 ± 4.9	9 ± 2.4	10 ± 2.7
	333	25 ± 6.2	6 ± 0.6	6 ± 1.2
	1,000	28 ± 5.5	10 ± 3.1	9 ± 2.5
	3,333	26 ± 2.8	7 ± 1.0	7 ± 0.9
	10,000	22 ± 2.7	10 ± 3.1	12 ± 1.5
TA1537	0	4 ± 0.6	9 ± 2.1	6 ± 0.9
	100	4 ± 0.7	9 ± 2.1	5 ± 1.2
	333	3 ± 0.9	7 ± 2.6	6 ± 1.2
	1,000	3 ± 0.7	9 ± 2.5	8 ± 0.7
	3,333	4 ± 0.7	5 ± 2.0	10 ± 2.3
	10,000	3 ± 0.9	6 ± 2.0	11 ± 1.0
TA98	0	16 ± 1.2	31 ± 1.5	26 ± 5.3
	100	13 ± 2.3	25 ± 2.3	28 ± 0.3
	333	17 ± 1.8	31 ± 3.2	38 ± 0.9
	1,000	13 ± 0.0	30 ± 2.8	31 ± 1.3
	3,333	12 ± 2.3	28 ± 1.5	35 ± 1.8
	10,000	18 ± 3.0	32 ± 3.2	34 ± 1.5

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced animals (male Sprague-Dawley rats or male Syrian hamsters). Cells and test compound or solvent (DMSO) were incubated for 20 min at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube was poured onto minimal medium, and the plates were incubated at 37° C for 48 h (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE L2. MUTAGENICITY OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound (Dose)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Water				
	92	91.5	100	34
	104	109.3	100	32
	136	112.7	100	40
	167	106.0	100	53
Ethyl methanesulfonate				
(5 µg)	683	79.3	44.7	287
	676	95.0	66.9	237
	663	118.3	81.5	187
Dimethyl morpholinophosphoramidate				
(1,712 µg/ml)	154	84.0	50.2	61
	141	92.5	56.9	51
	158	104.7	78.6	50
(1,957 µg/ml)	136	80.3	40.1	56
	135	88.7	59.0	51
	157	73.8	46.4	71
(2,200 µg/ml)	143	106.0	50.3	45
	196	84.5	22.7	77
	206	74.7	47.1	92
(2,324 µg/ml)	317	100.8	32.4	105
	288	75.0	28.5	128
	211	94.5	42.7	74
(2,446 µg/ml)	201	96.2	49.0	70
	253	89.2	49.6	95
	287	105.3	48.4	91
(2,690 µg/ml)	331	95.0	9.9	116
	189	106.2	64.3	59
	262	91.8	48.7	95

(a) Experiments were performed twice; all doses were tested in triplicate, except the solvent control (water), which was tested in quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 h at 37° C in medium, washed, and resuspended in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE L3. SISTER-CHROMATID EXCHANGES (SCE'S) OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CHINESE HAMSTER OVARY (CHO) CELLS (a)

−S9		+S9 (b)	
Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	SCE/Cell
Medium	7.58	Medium	8.52
1,000	10.40	1,600	9.86
1,600	12.74	3,000	9.76
3,000	15.26	4,000	9.40
4,000	15.88	5,000	9.56
5,000	21.22		
Mitomycin C		Cyclophosphamide	
0.005	25.12	1.5	21.34

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 h at 37° C. Then BrdU was added and incubation continued for 24 h. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1μg/ml) was added, and incubation was continued for 2-3 h. Cells were then collected by mitotic shake-off, treated for 3 min with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978). In the presence of S9, cells were incubated with test compound or solvent for 2 h at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 h, with colcemid (0.1 μg/ml) present for the final 2-3 h.
(b) S9 from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE L4. CHROMOSOMAL ABERRATIONS OF DIMETHYL MORPHOLINOPHOSPHORAMIDATE IN CHINESE HAMSTER OVARY (CHO) CELLS (a)

−S9		+S9 (b)	
Dose (μg/ml)	Aberration/100 cells (percent cells with aberrations)	Dose (μg/ml)	Aberration/100 cells (percent cells with aberrations)
Medium	1 (1)	Medium	1 (1)
2,000	3 (3)	2,000	3 (3)
3,000	4 (4)	3,000	5 (5)
4,000	7 (6)	4,000	5 (5)
5,000	16 (11)	5,000	2 (2)
Mitomycin C		Cyclophosphamide	
0.5	52 (39)	50	50 (38)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 h at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1μg/ml) was added. After another 2-3 h of incubation, cells were collected by mitotic shake-off, fixed, and stained in 6% Giemsa. In the presence of S9, cells were incubated with test compound or solvent for 2 h at 37° C. Cells were then washed, medium was added and incubation continued for 8-10 h. Colcemid (0.1 μg/ml) was added for the final 2-3 h; then the cells were collected and fixed as above.
(b) S9 from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

APPENDIX M

INGREDIENTS, NUTRIENT COMPOSITION, AND MEASURED CONTAMINANT LEVELS OF THE NIH 07 DIET

Pelleted Diet: March 1980 to April 1982

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE M1. INGREDIENTS OF THE NIH 07 DIET (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2. VITAMINS AND MINERALS IN THE NIH 07 DIET (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D activated animal sterol
d-A-tocopheryl acetate	20,000 IU	
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	d-Calcium pantothenate
Folic acid	2.2 g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
B_{12}	4,000 µg	
Biotin	140.0 mg	d-Biotin
K_3	2.8 g	Menadione activity
Choline	560.0 g	Choline chloride
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE M3. NUTRIENT COMPOSITION OF THE NIH 07 DIET (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.14 ± 0.88	22.7-25.1	24
Crude fat (percent by weight)	4.77 ± 0.34	4.1-5.4	24
Crude fiber (percent by weight)	3.31 ± 0.50	1.4-4.3	24
Ash (percent by weight)	6.67 ± 0.49	5.83-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,700 ± 2,350	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
A-tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.4 ± 4.5	7.3-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.32 ± 0.20	0.81-1.69	24
Phosphorous (percent)	1.01 ± 0.08	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of diet analyzed for nutrients in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE M4. CONTAMINANT LEVELS OF THE NIH 07 DIET

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.38 ± 0.23	<0.05-1.06	24
Cadmium (ppm) (a)	0.11 ± 0.07	<0.01-0.40	24
Lead (ppm)	0.91 ± 0.51	0.50-2.65	24
Mercury (ppm) (b)	< 0.05		
Selenium (ppm)	0.30 ± 0.09	0.10-0.52	24
Aflatoxins (ppb) (b,c)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (d,e)	7.17 ± 3.66	<0.1-13.0	24
Nitrite nitrogen (ppm) (d,e)	1.88 ± 1.58	<0.1-6.9	24
BHA (ppm) (f,g)	4.39 ± 3.72	<0.4-13.0	24
BHT (ppm) (f)	2.67 ± 1.50	0.8-5.9	24
Aerobic plate count (CFU/g) (h)	45,008 ± 33,225	5,500-120,000	24
Coliform (MPN/g) (i)	36.4 ± 52.5	<3-240	23
Coliform (MPN/g) (j)	125 ± 304	<3-1,100	24
E. Coli (MPN/g) (k)	<3		24
Total nitrosamines (ppb) (l,m)	7.16 ± 6.92	0.8-24.5	21
Total nitrosamines (ppb) (l,n)	29.36 ± 64.76	0.8-273	24
N-Nitrosodimethylamine (ppb) (l,m)	5.54 ± 6.03	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (l,n)	27.55 ± 64.41	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.34 ± 0.93	0-3.5	24
Pesticides (ppm)			
Alpha BHC (b,o)	<0.01		24
Beta BHC (b)	<0.02		24
Gamma BHC-Lindane (b)	<0.01		24
Delta BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (b)	<0.01		24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (b,p)	<0.05	0.09 (8/26/81)	24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCB's (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (b,p)	<0.1	0.2 (4/27/81)	24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (q)	0.09 ± 0.07	<0.05-0.27	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

TABLE M4. CONTAMINANT LEVELS OF THE NIH 07 DIET (Continued)

(a) Two batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, given in the table as the mean.
(c) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(d) Source of contamination: Alfalfa, grains, and fish meal
(e) Two batches contained less than 0.1 ppm.
(f) Source of contamination: Soy oil and fish meal
(g) Three batches contained less than 0.5 ppm.
(h) CFU = colony-forming unit
(i) Excludes one very high value of 1,100 obtained in batch produced on 12/16/80
(j) Includes the high value listed in footnote i
(k) All values were less than 3 MPN/g. MPN = most probable number.
(l) All values were corrected for percent recovery.
(m) Mean, standard deviation, and range exclude three very high values in the range of 115-280 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(n) Mean, standard deviation, and range include the very high values given in footnote m.
(o) BHC = hexachlorocyclohexane or benzene hexachloride
(p) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(q) Twelve batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and draft NTP Technical Report on the 2-year gavage studies of dimethyl morpholinophosphoramidate (DMMPA) in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The 2-year studies were conducted by Litton Bionetics, Inc. The rats were placed on study in April 1980 and were killed in May 1982. The mouse studies were started in May 1980. Because of early mortality, all of the male mice were killed in November 1980. The male mouse study was restarted in January 1981, and the animals were killed in January 1983. The female mice were killed in May 1982. All studies were begun before the NTP's requirement in October 1981 for full compliance with Good Laboratory Practice procedures.

The audit of these studies was conducted by the National Toxicology Program and ImmuQuest Laboratory, Inc., from July 2 to July 20, 1984. NTP audit team members were Dr. P. Chan, Ms. C. Davies, Dr. S. Eustis, and Dr. C. Whitmire. ImmuQuest audit team members were Dr. L. Brennecke, Ms. P. Errico, Mr. D. Haynes, Ms. C. Reese, and Dr. K. Whitkin. The full report of the audit of DMMPA is on file at the NTP Archives, Research Triangle Park, North Carolina, and is available upon request.

In-life toxicology data examined included the study protocol, the internal memoranda, records of telephone conversations, animal shipment receipts, dates of birth, animal conditions upon receipt, animals killed because of disease and parasites, method of randomizing animals and assigning them to cages and dose groups, method of animal identification (ear tag, cage card, toe clip/ear punch), conditions of the animals during and at the end of the quarantine period, animal body weights, chemical mixing data and quantities prepared, dose calculations, dosing records, clinical observations, correlation of clinical observation and gross observation on Individual Animal Data Records, moribundity and mortality records, temperature and humidity of the animal rooms, cage and rack cleaning and arrangement/rotation schedules, feeding log, bedding material, water analyses, and sentinel animal data. The audit review found that the in-life data were complete and all observations and events were accurately documented. There were no problems with the execution of studies or with the collection or reporting of data.

A random 10% of the pathology records for rats and mice were examined for readability of animal number identification, correlation of gross lesions and microscopic diagnosis, tissue accountability, slide/block match, data entry errors, disposition code errors, and correlation of diagnosis on Individual Animal Pathology Table and Individual Animal Data Records; wet tissues were checked for possible missed lesions. Clinical signs and tumors were tracked by examining the wet tissues of 10 animals (20%) chosen at random from each group of rats and mice in the studies. The audit review of the pathology data revealed a few discrepancies, all of which were considered minor and inconsequential to the findings.

Analytical chemistry data examined included bulk chemical characterization, purity, stability, dose preparations, chemical/vehicle analyses, and corn oil vehicle peroxide analyses. The analytical chemistry data showed that the purity and chemical/vehicle analyses were appropriately conducted and the animals received the prescribed dose of DMMPA.

In conclusion, the audit findings indicated that the 2-year studies of DMMPA in rats and mice were conducted properly. No discrepancies that might have affected the final interpretation of the study were noted. The data examined in the audit are considered adequate to meet the objectives of the study.