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TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (CAS NO. 868-85-9) 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 HYDROGEN PHOSPHITE

(CAS NO. 868-85-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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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).

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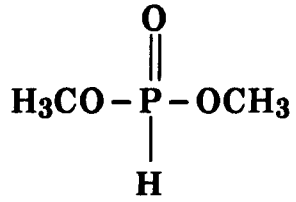

DIMETHYL HYDROGEN PHOSPHITE

CAS No. 868-85-9

Molecular Weight 110.6 Molecular Formula $C_2H_7O_3P$

Synonyms:

Phosphonic acid, dimethyl ester (9CI)	TL 585
Dimethyl phosphite	DMHP
Dimethyl phosphorus acid	Phosphorous acid, dimethyl ester
Methyl phosphonate	Dimethylphosphite
Dimethyl phosphonate	Dimethylphosphonate
Dimethoxyphosphine oxide	Dimethylphosphorous acid
	Bis (hydroxymethyl) phosphine oxide

ABSTRACT

Dimethyl hydrogen phosphite (DMHP) is used as an intermediate in the production of insecticides and herbicides, as an additive to lubricants, and as a stabilizer in oil and plaster and was considered for use as a chemical to simulate the physical (but not the biologic) properties of anticholinesterase agents. Results of 13-week gavage studies in F344/N rats (0-400 mg DMHP/kg body weight) and in $B6C3F_1$ mice (0-1,500 mg DMHP/kg body weight) were used to identify short-term toxicity and to establish doses for the 2-year toxicology and carcinogenesis studies. In these studies, dimethyl hydrogen phosphite (greater than 97% pure) was administered for 103 weeks in corn oil by gavage to groups of 50 male F344/N rats and to groups of 50 male and 50 female $B6C3F_1$ mice at doses of 0, 100, or 200 mg/kg and to groups of 50 female F344/N rats at doses of 0, 50, or 100 mg/kg.

In the 2-year studies, survival of high dose male rats and high dose male mice was lower ($P<0.05$) than that of the vehicle controls (male rats: vehicle control, 39/50; low dose, 29/50; high dose, 23/50; male mice: 42/50; 34/50; 32/50). At the end of the studies, mean body weights were lower than those of the corresponding vehicle controls for high dose male rats (–15%), for high dose female rats (–5%), and for high dose male mice (–5%).

Dimethyl hydrogen phosphite caused dose-related increases in nonneoplastic and neoplastic lesions of the lung in male and female rats. In high dose male rats, there were increased incidences of lung neoplasms, including squamous cell carcinomas (0/50; 0/50; 5/50), alveolar/bronchiolar adenomas (0/50; 0/50; 5/50), and alveolar/bronchiolar carcinomas (0/50; 1/50; 20/50). In high dose female rats, there was a marginal increase in the incidence of alveolar/bronchiolar carcinomas of the lung (0/50; 1/49; 3/50). Hyperplasia of the lung and chronic interstitial pneumonia were increased in dosed male rats and in high dose female rats.

Dimethyl hydrogen phosphite caused increases in forestomach lesions in male and female rats. In male rats, there was an increased incidence of forestomach neoplasms, including squamous cell papillomas (0/50; 1/50; 3/50) and squamous cell carcinomas (0/50; 0/50; 3/50). High dose male rats had increased incidences of hyperkeratosis and hyperplasia of the forestomach. In high dose female rats,

the incidence of forestomach hyperplasia was increased. Neoplastic lesions of the forestomach (a squamous cell papilloma and a squamous cell carcinoma) were found in two high dose female rats.

Mineralization of the cerebellum was seen in high dose male rats (12/49) and in no other group. Focal calcification of the testis occurred at increased incidence in dosed male mice in the 2-year studies (2/50; 9/47; 24/50). Compound-related testicular atrophy was seen in male mice in the 13-week study.

Dimethyl hydrogen phosphite did not induce any neoplasms in male or female mice.

Dimethyl hydrogen phosphite was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. This chemical did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*.

An audit of the experimental data was conducted for these carcinogenesis studies on dimethyl hydrogen phosphite. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these gavage studies, there was *clear evidence of carcinogenicity** in male F344/N rats receiving dimethyl hydrogen phosphite, as shown by increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and squamous cell carcinomas of the lung and of neoplasms of the forestomach. There was *equivocal evidence of carcinogenicity* in female F344/N rats receiving dimethyl hydrogen phosphite, as shown by marginally increased incidences of alveolar/bronchiolar carcinomas of the lung and of neoplasms of the forestomach. There was *no evidence of carcinogenicity* in male or female $B6C3F_1$ mice receiving dimethyl hydrogen phosphite at doses of 100 or 200 mg/kg for 103 weeks.

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

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The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dimethyl Hydrogen Phosphite is based on 13-week studies that began in December 1978 and ended in March 1979 and on 2-year studies that began in March 1980 and ended in April 1982 at Litton Bionetics, Inc.

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The members of the Peer Review Panel who evaluated the Technical Report on dimethyl hydrogen phosphite on July 27, 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.

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*Unable to attend meeting

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

On July 27, 1984, the Technical Report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite (DMHP) 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 with the conclusions as written. He asked for more discussion of the possible pathogenesis of the rat lung lesions, including the high incidence of interstitial pneumonia [see p. 38]. He said that the experimental design could have been improved by the inclusion of other indicators of toxicity, such as serum enzymes, organ weights, hematology, and urinalyses.

As a second principal reviewer, Dr. Davis agreed with the conclusions and suggested that a statement be added to the abstract concerning the compound-related testicular atrophy in male mice in the 13-week study and focal calcification of the testis in male mice in the 2-year study [see p. 12]. She agreed with Dr. Kociba for expanded discussion of the lung lesions in rats as well as the dose-related lung lesions in male and female mice in the 13-week studies.

As a third principal reviewer, Dr. Tannenbaum agreed with the conclusions and concurred with the comments of the other reviewers. He wondered if the high incidence of pneumonia, especially if infectious, might not have compromised the conclusions. Dr. G. Boorman, NTP, explained that the pneumonia was chemically induced and not infectious in origin. The lesions in dosed animals were not inflammatory but were characterized as hyperplasias of the alveolar epithelium around the smaller bronchioles and the terminal bronchioles; this description would be expanded and clarified in the report. [See p. 38.]

Dr. Van Ryzin questioned the conclusion pertaining to neoplasms of the forestomach in support of equivocal evidence of carcinogenicity in female rats. Dr. J. Haseman, NIEHS, replied that even though there were only two neoplasms at the high dose, this incidence was similar to that seen in the low dose males that received the same dose on a milligram per kilogram basis as did the high dose females.

Dr. Davis moved that the Technical Report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite be accepted with the minor changes discussed. Dr. Kociba seconded the motion, and the report was approved unanimously by the Peer Review Panel.

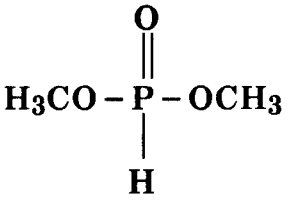
I. INTRODUCTION

Production and Use

Toxicity and Mutagenicity

Study Rationale

I. INTRODUCTION



DIMETHYL HYDROGEN PHOSPHITE

CAS No. 868-85-9

Molecular Weight 110.6 Molecular Formula $C_2H_7O_3P$

Synonyms:

Phosphonic acid, dimethyl ester (9CI)	TL 585
Dimethyl phosphite	DMHP
Dimethyl phosphorus acid	Phosphorous acid, dimethyl ester
Methyl phosphonate	Dimethylphosphite
Dimethyl phosphonate	Dimethylphosphonate
Dimethoxyphosphine oxide	Dimethylphosphorous acid
	Bis (hydroxymethyl) phosphine oxide

Production and Use

Dimethyl hydrogen phosphite (DMHP), a colorless liquid, is a neutral ester of phosphorous acid. DMHP is used as an intermediate in the production of insecticides and herbicides, as an additive to lubricants, and as a stabilizer in oil and plaster (Siemer, 1980; Lewis, 1975). The U.S. Army selected dimethyl hydrogen phosphite as a candidate for simulating the physical (but not biologic) properties of anticholinesterase nerve agents; it is no longer being considered for this use (U.S. Air Force, personal communication to J. Dunnick, 1982). Approximately 3 million pounds are produced per year (W. Smithey, Jr., personal communication to J. Dunnick, 1982). More current production figures are not available from other sources (USITC, 1983).

Toxicity and Mutagenicity

Oral LD_{50} values of 3,050 to 4,250 mg/kg have been reported for rats of unspecified sex or strain (NIOSH, 1981; Mobil, 1977). No information on the toxicology or carcinogenicity of DMHP was located (NLM, 1984).

Dimethyl hydrogen phosphite was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without Aroclor 1254-induced Sprague-Dawley or Syrian hamster liver metabolic activation (Appendix K). DMHP also did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*.

Study Rationale

Dimethyl hydrogen phosphite was nominated in 1976 by the U.S. Army for carcinogenesis testing because it was a candidate to simulate the physical (but not the biologic) properties of anticholinesterase agents. Additional information on the proposed use of this compound is not available. Recently, toxicology and carcinogenesis studies have been completed on three other simulants: tris(2-ethylhexyl)phosphate (NTP, 1984), dimethyl morpholinophosphoramidate (DMMPA; NTP, 1985), and dimethyl methylphosphonate (DMMP). All four chemicals were administered by gavage in corn oil. This vehicle was chosen because of the potential for chemical hydrolysis in water.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHYL HYDROGEN PHOSPHITE
PREPARATION AND ANALYSIS OF DOSE MIXTURES
SINGLE-ADMINISTRATION STUDIES
FIFTEEN-DAY REPEATED-ADMINISTRATION 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 HYDROGEN PHOSPHITE

Dimethyl hydrogen phosphite was obtained from the U.S. Army Chemical Systems Laboratory (Aberdeen Proving Grounds, Aberdeen, Maryland) in two lots. Lot no. DM113077 was used for the single-administration, 15-day repeated-administration, and 13-week studies. Lot no. KC031247 was used for the 2-year studies.

Both lots of test chemical were identified as dimethyl hydrogen phosphite by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Appendix G). All spectra were consistent with the structure of the chemical; the infrared and nuclear magnetic resonance spectra were consistent with literature spectra.

Cumulative data indicated that lot no. DM113077 was approximately 96% pure. This purity estimation was based on elemental analyses that agreed with theoretical values and chromatographic data. Thin-layer chromatography detected a slight trace impurity and a very slight trace impurity by one system; a trace impurity was detected by a second system. Gas chromatography detected 10 impurities totaling 3.91% of the major peak on one system and 8 impurities totaling 3.87% of the major peak area on a second system. Two impurities with areas of 1.0% or greater relative to that of the major peak were detected by each gas chromatographic system.

Cumulative data indicated that lot no. KC031247 was approximately 97%-98% pure. This purity estimation was based on elemental analyses, in which the values for carbon and hydrogen agreed with the theoretical values but the value for phosphorus was 98.4% of the theoretical; a titration value of 97.5% ± 0.3% based on reaction with excess sodium hydroxide; and chromatographic data. Thin-layer chromatography by two systems indicated no impurities. Gas chromatography detected seven impurities totaling 2.3% of the major peak on one system and four impurities totaling 1.9% of the major peak on a second system. An impurity with an area of 1.1% relative to that of the major peak was detected by each gas chromatographic system and identified as trimethyl phosphate.

Dimethyl hydrogen phosphite was found to be stable when stored in sealed containers at temperatures up to 60° C for 2 weeks; gas chromatography was used to monitor stability (Appendix G). The testing laboratory (Litton Bionetics, Inc.) stored several portions at −20° C as reference samples and the remainder at room temperature. Periodic reanalyses of the test and reference samples at the testing laboratory by infrared spectroscopy and gas chromatography indicated no deterioration of the chemical over the course of the studies.

PREPARATION AND ANALYSIS OF DOSE MIXTURES

Dimethyl hydrogen phosphite and corn oil were mixed to yield desired concentrations. Dimethyl hydrogen phosphite (1% w/w) in corn oil was stable when stored at room temperature for 7 days (Appendix H). Dimethyl hydrogen phosphite/corn oil mixtures were stored at room temperature for no longer than 7 days.

Analyses for dimethyl hydrogen phosphite in corn oil were performed on every eighth dose mixture to confirm that the correct concentrations were administered to the test animals. The method of analysis involved a methanolic extraction as a purification step and a gas chromatographic assay as a quantitation step (Appendix I). In addition, samples were sent to the analytical chemistry laboratory for referee analysis twice each year during the 2-year studies (Appendix J, Table J2). Because 40/46 samples tested were within 10% of the target concentations, the corn oil mixtures were estimated to have been within specifications 87% of the time (Table 1 and Appendix J, Table J1).

TABLE 1. SUMMARY OF ANALYSES OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

	Target Concentration (mg/ml)		
	12.5	25.0	50.0
Mean (mg/ml)	12.9	25.9	51.7
Standard deviation	1.37	1.46	3.08
Coefficient of variation (percent)	10.6	5.6	6.0
Range (mg/ml)	11.2-16.5	23.4-29.1	47.0-59.2
Number of samples	14	16	16

SINGLE-ADMINISTRATION STUDIES

Single-administration studies were conducted to evaluate acute toxicity and to determine doses for the 15-day repeated-administration studies. Male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and observed for 2 weeks before the study began.

Groups of five males and five females of each species were administered a single dose of 1,470, 2,150, 3,160, 4,640, or 6,810 mg/kg dimethyl hydrogen phosphite in corn oil (5.675 ml/kg body weight) by gavage. Rats and mice were fasted overnight before dosing. All animals were observed for mortality immediately after dosing, 4 hours later, and then one time per day for 14 days; they were killed on day 15 or 16; no body weights were taken. Necropsies were performed on all animals; no histopathologic examinations were performed. Details of animal maintenance are given in Table 2.

FIFTEEN-DAY REPEATED-ADMINISTRATION STUDIES

Fifteen-day repeated-administration studies were conducted to determine doses for the 13-week studies. Male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and held for 2-3 weeks before the studies began.

Groups of five males and five females of each species were administered 0, 250, 500, 1,000, 2,000, or 3,000 mg/kg (mice only) dimethyl hydrogen phosphite in corn oil by gavage daily for 15 consecutive days. The 3,000 mg/kg group of rats was administered undiluted dimethyl hydrogen phosphite.

Animals were housed five per cage and received water (acidified to pH 2.5 with hydrochloric acid) and feed ad libitum. Further details of animal maintenance are presented in Table 2. The rats and mice were observed two times per day for mortality and were weighed on days 0 and 15 (mice) or on day 0 (rats). Initial (but not final) body weights were taken for rats. Necropsies were performed on all animals. No histopathologic examinations were performed on rats. Only the stomach was examined histopathologically in mice.

THIRTEEN-WEEK STUDIES

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

Four- to five-week-old male and female F344/N rats and 4- to 6-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days, and assigned to cages according to a table of random numbers. The cages were then assigned to dosed and vehicle control groups according to another table of random numbers.

Groups of 10 rats of each sex were administered 0, 25, 50, 100, 200, or 400 mg/kg dimethyl hydrogen phosphite 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 95, 190, 375, 750, or 1,500 mg/kg. Animals were checked two times per day for signs of moribundity and mortality; moribund animals were killed. Animal weights were recorded weekly. Further experimental details are summarized in Table 2.

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

	Single-Administration Studies	Fifteen-Day Repeated-Administration Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Testing Laboratory	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	1,470, 2,150, 3,160, 4,640, or 6,810 mg/kg dimethyl hydrogen phosphite in corn oil by gavage; dose vol--5.675 ml/kg	0, 250, 500, 1,000, 2,000, or 3,000 mg/kg (mice only) dimethyl hydrogen phosphite in corn oil by gavage; (3,000 mg/kg dose for rats administered as undiluted dimethyl hydrogen phosphite) dose vol--10 ml/kg (mice), 2.5 ml/kg (rats)	Rats--0, 25, 50, 100, 200, or 400 mg/kg dimethyl hydrogen phosphite in corn oil by gavage; mice--0, 95, 190, 375, 750, or 1,500 mg/kg; dose vol--3.33 ml/kg	Male rats and all mice--0, 100, or 200 mg/kg dimethyl hydrogen phosphite in corn oil by gavage; female rats--0, 50, or 100 mg/kg; dose vol--4.0 ml/kg
Date of First Dose	Rats--8/9/78; mice--8/2/78	Rats--8/31/78; mice--9/18/78	12/27/78	Rats--3/13/80; mice--4/3/80
Date of Last Dose	N/A	Rats--9/14/78; mice--10/2/78	Rats--3/26/79; mice--3/23/79	Rats--3/5/82; mice--3/26/82
Duration of Dosing	One time only	15 consecutive days	5 d/wk for 13 wk	5 d /wk for 103 wk
Type and Frequency of Observation	Observed immediately after dosing, 1 h and 4 h later, and 1 × d thereafter for 14 d	Observed 2 × d for mortality	Observed 2 × d for signs of moribundity and mortality	Observed 2 × d for signs of moribundity and mortality; weighed 1 × wk for 13 wk, 1 × 4 wk thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals	Necropsy performed on all animals; stomach lesions examined microscopically (mice)	Necropsy performed on all animals; the following tissues from vehicle control and 400 mg/kg group of rats and vehicle control and all but the 95 mg/kg dosed group of mice microscopically examined: gross lesions, skin (mice), parathyroids, colon, esophagus, brain, sternebrae (including marrow), liver, lung and mainstem bronchi, stomach, thymus, pancreas, kidney, urinary bladder, eyes, mandibular lymph node, salivary glands, thyroid gland, small intestine, ovaries/uterus or prostate (mice)/testes, heart, trachea, spleen, adrenal glands, pituitary gland, gallbladder (mice), mammary gland. Only heart, liver, and kidney examined for the 95 mg/kg group of mice. Eyes of vehicle control and 200 mg/kg groups of rats examined	Necropsy performed on all animals. Tissues examined microscopically: tissue masses and gross lesions, regional lymph node, skin, blood smear, mandibular lymph node, mammary gland, salivary glands, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, mesenteric lymph node, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes, or ovaries/uterus, nasal cavity, brain, pituitary gland, eyes, and spinal cord

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (Continued)

	Single-Administration Studies	Fifteen-Day Repeated Administration Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animal Identification Method	Not specified	Ear punch or notch	Rat--ear tag; mice--ear notch	Rat--ear tag; mice--ear notch, toe clip
Time Held Before Test	2 wk	Rats--2 wk; mice--18 d	2 wk	2 wk
Age When Placed on Study	Rats--6 wk; mice--5-6 wk (exact age not stated)	Rats--43 d; mice--approx 6 wk (exact age not stated for mice)	Rats--6-7 wk; mice--6-8 wk	Rats--7 wk; mice--6-8 wk
Age When Killed	Rats--8 wk; mice--7-8 wk	Rats--59 d; mice--8 wk	Rats--19-20 wk; mice--19-21 wk	Rats--111 wk; mice--110-112 wk
Necropsy Dates	Rats--8/24/78; mice--8/16/78	Rats--9/15/78; mice--10/3/78	Rats--3/28-3/29/79; mice--3/26-3/27/79	Rats--3/15-3/18/82; mice--4/5-4/8/82
Method of Animal Distribution	Assigned to cages so that average cage weights for each sex and species were approximately equal	Same as single-administration studies	Assigned to cages according to a table of random numbers; cages then assigned to groups according to another table of random numbers	Same as 13-wk studies
Feed	Purina Lab Chow® meal (St. Louis, MO); available ad libitum	Same as single-administration studies	Purina Lab Chow® pellets (St. Louis, MO)	NIH 07 Open Formula (Zeigler Bros, Gardners, PA); available ad libitum
Bedding	Ab-Sorb-Dri® hardwood chips (Williams Feed and Bedding, Gaithersburg, MD)	Same as single-administration studies	Same as single-administration studies	Ab-Sorb-Dri® hardwood chips, then Sani-Chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)
Water	Acidified with HCl (pH 2.5) tap water; available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Polycarbonate (Lab Products, Inc., Garfield or Rochelle Park, NJ, and Hazleton Systems, Aberdeen, MD)
Cage Filters	Nonwoven polyester filter sheets (Snow Filtration, Co., Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage	5	5	5	5

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (Continued)

	Single-Administration Studies	Fifteen-Day Repeated-Administration Studies	Thirteen-Week Studies	Two-Year Studies
Animal Room Environment	Not reported	Not reported	Temp--22°-24° C; humidity--30%-70%; fluorescent light 12 h/d; 15 room air changes/h	Temp--22°-24° C (maximum 28° C); humidity--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h
Other Chemicals on Test in Same Room	Dimethyl methylphosphonate	Same as single-administration studies	None	None
CHEMISTRY				
Lot Numbers Used	DM113077	DM113077	DM113077	KC031247
Date of Initial Use of Subsequent Lot	N/A	N/A	N/A	N/A
Supplier	U.S. Army Chemical Systems Laboratory (Aberdeen, MD)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
CHEMICAL/ VEHICLE				
Preparation	Appropriate amounts of dimethyl hydrogen phosphite and corn oil added by pipette to test tube; mixture was shaken for 1 min; mixtures resuspended before dosing	Highest rat dose undiluted; for all other doses, appropriate amounts of dimethyl hydrogen phosphite were mixed with corn oil on a vortex mixer for 2 min; mixtures resuspended before dosing	Appropriate amounts of dimethyl hydrogen phosphite mixed with corn oil; mixtures resuspended before dosing	Appropriate amounts of dimethyl hydrogen phosphite and corn oil mixed in a graduated cylinder by inversion; mixtures resuspended before dosing
Maximum Storage Time	N/A	3 d	Solutions prepared 1 × wk	7 d
Storage Conditions	N/A	Not specified	Not specified	Room temperature

At the end of the 13-week studies, survivors were killed. Necropsies were performed on all animals, except those excessively autolyzed or cannibalized. Tissues, groups examined histologically, and animal maintenance information are listed in Table 2.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats and 50 male and female mice were administered 0, 100, or 200 mg/kg dimethyl hydrogen phosphite in corn oil by gavage 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 50, or 100 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. Animals were shipped to the testing laboratory at 4-6 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 6-7 weeks of age and the mice, at 6-8 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 L).

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 electropherotograms 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 those 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 matched concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages and kept in the same animal room throughout the course of the studies. Feed and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum. The cages and the cage racks were not rotated during the studies. Details of animal maintenance are summarized in Table 2.

Clinical Examinations and Pathology

All animals were observed two times per day for signs of moribundity or mortality. Clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the studies 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 studies. 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 2.

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 PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and 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 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. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES
FIFTEEN-DAY REPEATED-ADMINISTRATION STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES
FIFTEEN-DAY REPEATED-ADMINISTRATION STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

Compound-related toxicity included inactivity, weakness, and shallow breathing on the day of dosing in animals receiving 3,160, 4,640, or 6,810 mg/kg. All the rats that received 4,640 or 6,810 mg/kg and 2/5 males and 3/5 females that received 3,160 mg/kg died on day 1 (Table 3). No other animals died. The LD_{50} values as determined by the Spearman-Karber method (Finney, 1978) were 3,283 mg/kg (95% confidence limits of 2,729-3,949 mg/kg) for male rats and 3,040 mg/kg (95% confidence limits of 2,527-3,656 mg/kg) for female rats. Necropsy findings included gas in the stomach and/or intestines in some of the animals receiving 3,160, 4,640, or 6,810 mg/kg. Based on these findings, the high dose for the 15-day repeated-administration studies was set at 3,000 mg/kg.

TABLE 3. SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

Dose (mg/kg)	Survival (b)
MALE	
1,470	5/5
2,150	5/5
3,160	3/5
4,640	0/5
6,810	0/5
FEMALE	
1,470	5/5
2,150	5/5
3,160	2/5
4,640	0/5
6,810	0/5

(a) Body weights were not recorded.
(b) Number surviving/number initially in the group; all deaths occurred on day 1.

FIFTEEN-DAY REPEATED-ADMINISTRATION STUDIES

All the rats that received 1,000, 2,000, or 3,000 mg/kg and 4/5 males and 2/5 females that received 500 mg/kg died before the end of the studies (Table 4). Rats that received 500 mg/kg or more were inactive after dosing. There were no dose-related findings at necropsy. Based on the mortality data and on the clinical signs, the high dose selected for the 13-week studies was 400 mg/kg.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIFTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (b) (grams)
MALE		
0	5/5	116
250	5/5	116
500	(c) 1/5	116
1,000	(d) 0/5	116
2,000	(e) 0/5	115
3,000	(f) 0/5	130
FEMALE		
0	5/5	95
250	5/5	91
500	(g) 3/5	93
1,000	(h) 0/5	93
2,000	(i) 0/5	92
3,000	(j) 0/5	92

(a) Number surviving/number initially in the group
(b) Final body weights were not recorded.
(c) Day of death: 8, 9, 11, 11
(d) Day of death: 4, 5, 6, 6, 6
(e) Day of death: 2, 3, 4, 4, 4
(f) All deaths occurred on day 3.
(g) All deaths occurred on day 13.
(h) Day of death: 5, 6, 6, 6, 7
(i) Day of death: 3, 3, 3, 3, 4
(j) Day of death: 1, 1, 2, 2, 2

THIRTEEN-WEEK STUDIES

Nine of 10 males and 8/10 females that received 400 mg/kg died before the end of the studies (Table 5). Three of the five deaths that occurred in the 100 and 200 mg/kg groups may have been due to the accidental introduction of gavage solutions into the lungs. Final mean body weights of males and females that received 400 mg/kg were depressed 46% and 39% relative to those of the vehicle controls. The final mean body weight of females that received 200 mg/kg was depressed 14% relative to that of the vehicle controls.

Degeneration of the lens was observed in the eyes of 4/9 females and 1/7 males that received 400 mg/kg. Acute diffuse inflammation of the cornea was observed in 1/9 females that received 400 mg/kg. The eyes of the next lower dose group (200 mg/kg) were examined histologically; eye lesions were not seen in either males (0/10) or females (0/9). (Eyes from all animals were not available for analysis due to autolysis.) Urinary bladder calculi were observed in 2/10 male rats that received 400 mg/kg.

Lesions were observed in the lungs of vehicle controls and all dosed groups (Table 6). Blood taken at the end of the studies was found to be positive by the hemagglutination inhibition assay for pneumonia virus and by the complement fixation assay for Sendai virus in 5/5 vehicle control females and 5/5 vehicle control males (Appendix L, Table L1).

Dose Selection Rationale: Based on survival and weight gain information, the doses for male rats in the 2-year study were set at 100 and 200 mg/kg and for female rats at 50 and 100 mg/kg. Doses for female rats were set lower than those for male rats because the females showed a more severe weight depression at 200 mg/kg in the 13-week studies.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Dose (mg/kg)	Survival (b)	Mean Body Weights (grams) (a) Initial	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	186	308	+122	--
25	10/10	185	290	+105	94.2
50	10/10	188	266	+ 78	86.4
100	10/10	194	314	+120	101.9
200	(d) 9/10	184	298	+114	96.8
400	(e) 1/10	184	168	- 16	54.5
FEMALE					
0	10/10	136	193	+ 57	--
25	10/10	137	195	+ 58	101.0
50	10/10	136	191	+ 55	99.0
100	(f) 8/10	138	185	+ 47	95.9
200	(g) 8/10	137	167	+ 30	86.5
400	(h) 2/10	135	117	- 18	60.6

(a) Only group weights were taken by laboratory; no individual animal weight data are available.
(b) Number surviving/number in group
(c) Mean weight change of the group
(d) Week of death: 10
(e) Week of death: 3, 4, 4, 5, 5, 7, 8, 9
(f) Week of death; 7, 11
(g) Week of death: 9, 12
(h) Week of death: 2, 3, 3, 3, 3, 4, 5, 8, 10

TABLE 6. NUMBERS OF RATS WITH HISTOPATHOLOGIC LESIONS IN THE EYE AND LUNG IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Lesion	Vehicle Control		100 mg/kg	200 mg/kg		400 mg/kg	
	Male	Female	Female	Male	Female	Male	Female
Eye							
No. animals examined microscopically	--	--	--	10	9	7	9
Degeneration, lens	--	--	--	--	--	1	4
Inflammation, chronic, diffuse cornea	--	--	--	--	--	--	1
Lung							
No. animals examined microscopically	10	10	2	1	2	10	10
Inflammation, chronic, focal	4	1	--	--	--	--	--
Inflammation, chronic, diffuse	3	2	--	--	1	5	6
Congestion	--	--	2	1	1	--	1
Congestion, diffuse	--	--	--	--	--	3	1
Congestion, acute	--	--	--	--	--	1	--
Histiocytosis	--	--	--	--	--	5	--

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5% lower than those of the vehicle control males after week 24 and 10% lower after week 40 (Table 7 and Figure 1). Low dose male rats and high dose female rats showed marginal depressions in weight gain compared with the corresponding vehicle controls; by the end of the studies, they weighed 4% to 5% less than the corresponding vehicle controls.

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Weeks on Study	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE	Vehicle Control		100 mg/kg			200 mg/kg		
0	139	50	143	102.9	50	135	97.1	50
1	168	50	173	103.0	50	170	101.2	50
2	199	50	203	102.0	50	198	99.5	50
3	227	50	228	100.4	50	224	98.7	50
4	249	50	253	101.6	50	247	99.2	50
5	257	50	257	100.0	50	250	97.3	50
6	277	50	281	101.4	50	272	98.2	50
7	291	50	294	101.0	50	288	99.0	50
8	303	50	307	101.3	50	301	99.3	50
9	315	50	318	101.0	50	312	99.0	50
10	327	50	329	100.6	50	321	98.2	50
11	332	50	334	100.6	50	324	97.6	50
12	341	50	344	100.9	50	335	98.2	50
13	350	50	353	100.9	50	344	98.3	50
16	369	50	369	100.0	50	363	98.4	50
20	387	50	389	100.5	50	379	97.9	50
24	391	50	391	100.0	50	377	96.4	50
28	410	50	408	99.5	50	387	94.4	49
32	416	49	418	100.5	50	382	91.8	49
36	424	49	424	100.0	50	386	91.0	49
40	440	49	440	100.0	50	400	90.9	49
44	456	48	451	98.9	50	410	89.9	49
48	461	48	454	98.5	48	414	89.8	49
52	468	48	461	98.5	48	419	89.5	48
56	474	48	465	98.1	46	423	89.2	48
60	480	48	469	97.7	44	425	88.5	48
64	483	48	476	98.6	43	430	89.0	46
68	490	47	481	98.2	41	432	88.2	46
72	493	46	479	97.2	41	433	87.8	46
76	494	46	477	96.6	40	432	87.4	46
80	493	45	476	96.6	40	432	87.6	44
84	487	45	473	97.1	37	429	88.1	42
88	493	44	474	96.1	37	431	87.4	41
92	488	43	470	96.3	36	424	86.9	38
96	489	42	465	95.1	35	424	86.7	34
100	479	40	459	95.8	32	413	86.2	30
104	468	39	451	96.4	29	399	85.3	23
FEMALE	Vehicle Control		50 mg/kg			100 mg/kg		
0	111	50	108	97.3	50	107	96.4	50
1	125	50	123	98.4	50	125	100.0	50
2	139	50	138	99.3	50	137	98.6	50
3	152	50	150	98.7	50	149	98.0	50
4	159	50	160	100.6	50	159	100.0	50
5	168	50	168	100.0	50	168	100.0	50
6	174	50	177	101.7	50	174	100.0	50
7	181	50	181	100.0	50	180	99.4	50
8	184	50	185	100.5	50	183	99.5	50
9	189	50	188	99.5	50	188	99.5	50
10	194	50	193	99.5	50	192	99.0	50
11	195	50	195	100.0	50	192	98.5	50
12	198	50	200	101.0	50	200	101.0	50
13	202	50	203	100.5	50	202	100.0	50
16	208	50	208	100.0	50	206	99.0	50
20	215	50	214	99.5	50	213	99.1	50
24	216	50	215	99.5	50	213	98.6	50
28	222	50	222	100.0	50	218	98.2	50
32	228	50	224	98.2	49	216	94.7	50
36	231	50	228	98.7	49	220	95.2	50
40	238	50	236	99.2	49	226	95.0	50
44	243	50	241	99.2	49	231	95.1	50
48	246	50	244	99.2	49	233	94.7	50
52	252	50	249	98.8	49	240	95.2	50
56	257	50	251	97.7	48	243	94.6	49
60	266	50	258	97.0	48	249	93.6	49
64	272	50	262	96.3	48	253	93.0	49
68	283	50	274	96.8	48	264	93.3	48
72	287	50	283	98.6	46	271	94.4	48
76	293	49	290	99.0	46	275	93.9	46
80	298	49	298	100.0	46	283	95.0	45
84	298	47	298	100.0	45	283	95.0	44
88	302	45	302	100.0	45	288	95.4	42
92	304	42	304	100.0	44	290	95.4	40
96	305	41	302	99.0	36	292	95.7	38
100	302	41	298	98.7	35	289	95.7	36
104	302	40	297	98.3	33	287	95.0	32

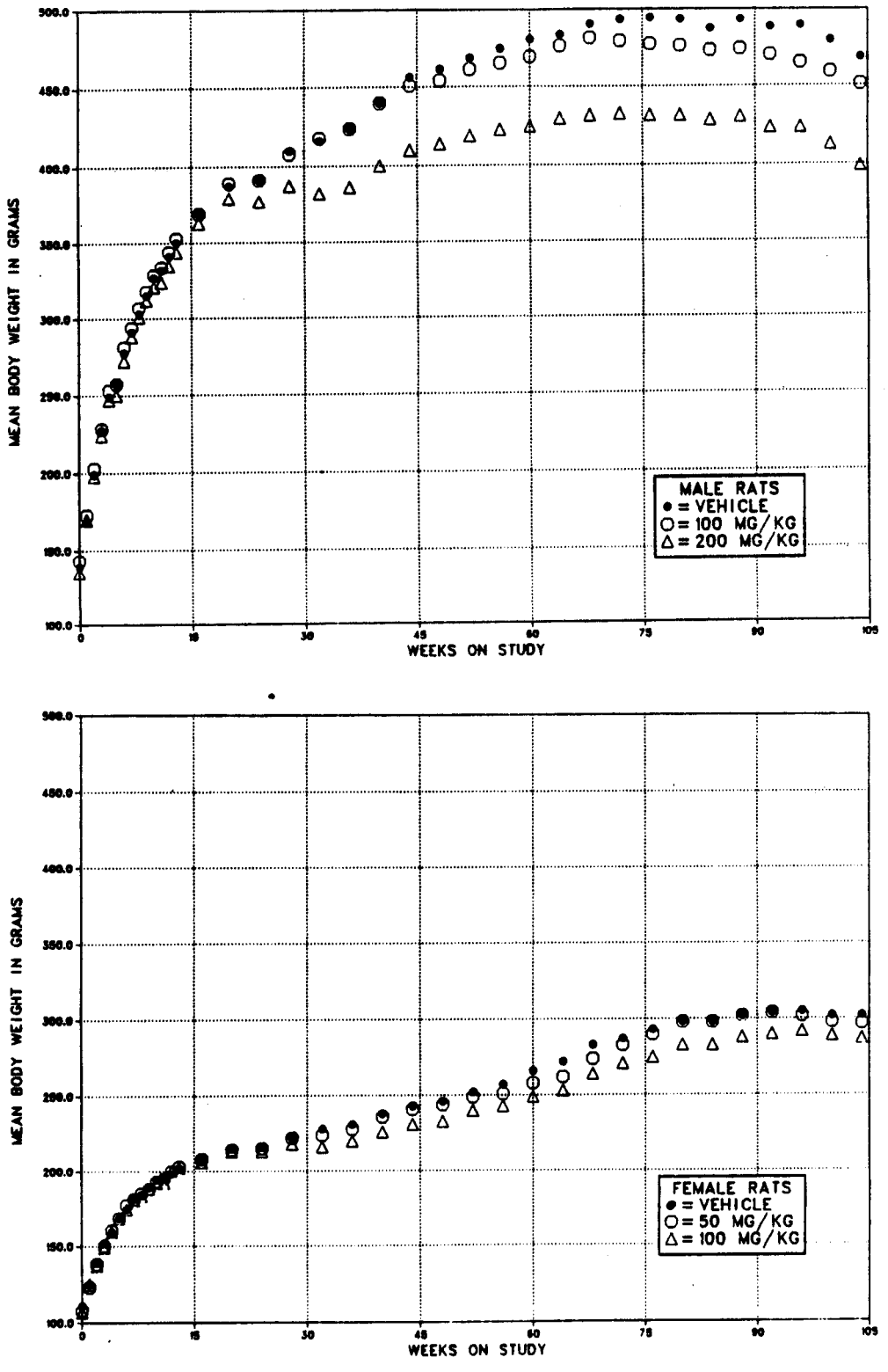


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED DIMETHYL HYDROGEN PHOSPHITE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats administered dimethyl hydrogen phosphite at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. Survival of female rats was comparable among all groups (Table 8). The survival of high dose male rats was significantly lower than that of the vehicle controls; the increased incidence of deaths in this group during the course of the experiment was attributed to the toxicity of the chemical.

Pneumonia was found in 0/10 vehicle control, 3/19 low dose, and 16/24 high dose male rats that died early in the study (nonaccidental deaths); thus, lung disease may have been a cause of the decreased survival in dosed male rats. Ten of 24 high dose male rats that died early in the study had lung tumors. The results of hemagglutination inhibition assays, complement fixation assays, and ELISA were negative for virus infection at 6, 12, 18, and 24 months (Appendix L, Table L2).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions in the lung, forestomach, hematopoietic system, eye, cerebellum, and liver. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives 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) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. Historical incidences of tumors in control animals are listed in Appendix F. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	19	24
Accidentally killed (c)	1	1	0
Killed at termination	39	29	23
Died during termination period	0	1	3
Survival P values (d)	0.009	0.061	0.008
	Vehicle Control	**50 mg/kg**	**100 mg/kg**
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	14	15
Accidentally killed (c)	0	1	1
Killed at termination	40	33	32
Died during termination period	0	2	2
Survival P values (d)	0.303	0.496	0.344

(a) Terminal kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) Deaths were due to gavage accidents.
(d) 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.

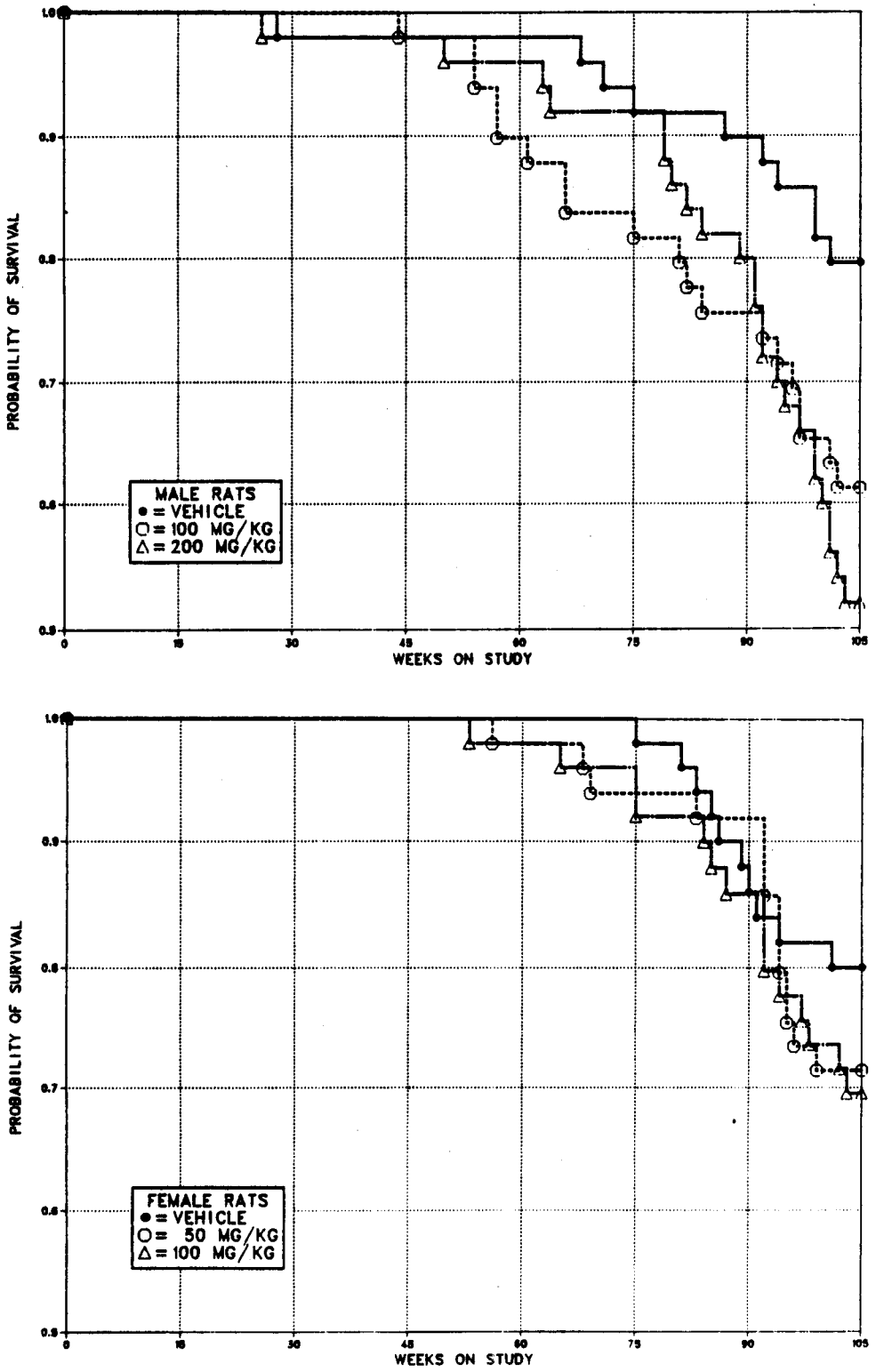


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DIMETHYL HYDROGEN PHOSPHITE IN CORN OIL BY GAVAGE FOR TWO YEARS

Lung: The incidences of nonneoplastic and neoplastic lung lesions were increased in dosed male and female rats (Table 9). The terms alveolar epithelium hyperplasia, adenomatous hyperplasia, and interstitial chronic pneumonia were used to diagnose a complex compound-related lesion characterized by hyperplasia of the alveolar epithelium and thickening of the septal walls around terminal bronchioles and adjacent alveoli. The lesion was compound related and most severe in the high dose animals. The incidence of inflammatory cells did not appear to be increased. The interstitial pneumonia diagnosed in the vehicle controls was very mild, did not have a centriacinar distribution, and usually consisted of a focal collection of histiocytes and/or mild perivascular cuffing of lymphocytes.

Adenomatous hyperplasia was a focal expansile lesion characterized by extensive proliferation of well-differentiated pneumocytes. This lesion was considered hyperplastic rather than neoplastic because the underlying supporting tissues of the lung remained intact and cytomorphologic evidence of neoplasia was lacking. The expansile nature of the lesion plus proliferative infoldings into alveolar spaces distinguished this lesion from the commonly observed focal hyperplasia of the alveolar epithelium. The latter is usually seen as a minimal or mild lesion following type I pneumocyte injury.

Squamous cell carcinomas, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and alveolar/bronchiolar adenomas or carcinomas (combined) in males and alveolar/bronchiolar carcinomas in females occurred with significant positive trends (Table 10). The incidences of squamous cell carcinomas, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male rats were significantly greater than those in the vehicle controls.

Alveolar/bronchiolar adenomas were characterized by focal areas of increased cellularity which caused compression of the adjacent parenchyma. The cells formed solid, glandular, or papillary patterns and obliterated the underlying alveolar structure. There was little cellular atypia, and mitotic figures were uncommon.

Compared with adenomas, alveolar/bronchiolar carcinomas showed more cellular atypia, invasion of adjacent lung parenchyma, and scirrhous response. On gross examination, the alveolar/bronchiolar carcinomas were yellow or white firm masses involving one or more lobes of the lung. Microscopically, these neoplasms were composed of polyhedric cells usually arranged in a papillary pattern, although tubular and solid trabecular patterns were also observed. Cellular atypism and invasion of surrounding tissues

TABLE 9. INCIDENCES OF LUNG LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

MALE	Vehicle Control	100 mg/kg	200 mg/kg
Hyperplasia, alveolar epithelium	2/50	7/50	16/50
Hyperplasia, adenomatous	0/50	3/50	26/50
Pneumonia, interstitial chronic	7/50	19/50	43/50
Metaplasia, squamous	0/50	0/50	3/50
Alveolar/bronchiolar adenoma	0/50	0/50	5/50
Alveolar/bronchiolar carcinoma	0/50	1/50	20/50
Squamous cell carcinoma	0/50	0/50	5/50
FEMALE	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Hyperplasia, alveolar epithelium	1/50	0/49	11/50
Hyperplasia, adenomatous	0/50	0/49	10/50
Pneumonia, interstitial chronic	4/50	5/49	33/50
Alveolar/bronchiolar carcinoma	0/50	1/49	3/50

TABLE 10. ANALYSIS OF LUNG TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

MALE	Vehicle Control	100 mg/kg	200 mg/kg
Squamous Cell Carcinoma (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	14.2%
Terminal Rates	0/39 (0%)	0/30 (0%)	1/26 (4%)
Life Table Tests	P=0.004	(c)	P=0.020
Incidental Tumor Tests	P=0.034	(c)	P=0.141
Alveolar/Bronchiolar Adenoma (d)			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	15.2%
Terminal Rates	0/39 (0%)	0/30 (0%)	2/26 (8%)
Life Table Tests	P=0.004	(c)	P=0.018
Incidental Tumor Tests	P=0.017	(c)	P=0.074
Alveolar/Bronchiolar Carcinoma (e)			
Overall Rates	0/50 (0%)	1/50 (2%)	20/50 (40%)
Adjusted Rates	0.0%	3.3%	63.5%
Terminal Rates	0/39 (0%)	1/30 (3%)	15/26 (58%)
Life Table Tests	P<0.001	P=0.448	P<0.001
Incidental Tumor Tests	P<0.001	P=0.448	P<0.001
Alveolar/Bronchiolar Adenoma or Carcinoma (f)			
Overall Rates	0/50 (0%)	1/50 (2%)	24/50 (48%)
Adjusted Rates	0.0%	3.3%	71.8%
Terminal Rates	0/39 (0%)	1/30 (3%)	17/26 (65%)
Life Table Tests	P<0.001	P=0.448	P<0.001
Incidental Tumor Tests	P<0.001	P=0.448	P<0.001
FEMALE	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Alveolar/Bronchiolar Carcinoma (g)			
Overall Rates	0/50 (0%)	1/49 (2%)	3/50 (6%)
Adjusted Rates	0.0%	2.9%	8.8%
Terminal Rates	0/40 (0%)	1/35 (3%)	3/34 (9%)
Life Table Tests	P=0.047	P=0.473	P=0.094
Incidental Tumor Tests	P=0.047	P=0.473	P=0.094

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at this laboratory: 0%; historical incidence in NTP studies: 2/1,143, 0.2% ± 0.58%
(c) No P value is presented because no tumors were observed in vehicle control and 100 mg/kg groups.
(d) Historical incidence at this laboratory: 2/150, 1.3% ± 1.2%; historical incidence in NTP studies: 34/1,143, 3.0% ± 1.9%
(e) Historical incidence at this laboratory: 3/150, 2.0% ± 0.0%; historical incidence in NTP studies: 16/1,143, 1.4% ± 1.5%
(f) Historical incidence at this laboratory: 5/150, 3.3% ± 1.2%; historical incidence in NTP studies: 50/1,143, 4.4% ± 2.4%
(g) Historical incidence at this laboratory: 1/150, 0.7% ± 1.2%; historical incidence in NTP studies: 10/1,142, 0.9% ± 1.3%

were consistent features. The alveolar/bronchiolar carcinomas metastasized to the mediastinal tissues in three high dose males and one low dose male. No metastases were seen in the female rats with carcinoma of the lung.

Five high dose male rats had lung tumors composed entirely of squamous cells. For this reason, these tumors were diagnosed as squamous cell carcinomas. The criteria for distinguishing proliferative lesions of the rat lung have been described by Boorman (1984). Squamous cell carcinomas appeared grossly as white to green lung masses. Microscopically, these lung masses were characterized by squamous differentiation, cellular atypia, and invasion of surrounding tissues. One of the animals with a squamous cell carcinoma also had an alveolar/bronchiolar carcinoma involving a separate lobe.

Interstitial pneumonia was found in 0/10 vehicle control, 4/19 low dose, and 18/24 high dose male rats that died early in the studies (nonaccidental deaths); thus, pulmonary changes may have contributed in part to the decreased survival in the dosed male rats. The interstitial pneumonia was characterized by centriacinar alveolar epithelial hyperplasia and thickening of septal walls. There did not appear to be an increased incidence of inflammatory cells; the lesion is considered to be compound related and noninfectious.

Forestomach: In male rats, there were proliferative lesions of the forestomach. Diffuse to focal thickening of the squamous epithelium was diagnosed as hyperplasia. Lesions characterized by papillary projections lined by squamous epithelium with fibrovascular cores were diagnosed as squamous cell papillomas. When the squamous cells invaded the submucosa, the lesions were diagnosed as squamous cell carcinomas. The squamous cell carcinomas were characterized by invasion of subjacent tissues and marked cellular atypia.

The incidences of hyperplasia in high dose rats of each sex and the incidence of hyperkeratosis in high dose males were greater than those in the vehicle controls (Table 11). Squamous cell papillomas, squamous cell carcinomas, and squamous cell papillomas or carcinomas (combined) in male rats occurred with significant positive trends (Table 12). The incidence of squamous cell papillomas or carcinomas (combined) in high dose males was significantly greater than that in the vehicle controls. Two forestomach neoplasms were seen in high dose female rats.

Hematopoietic System: The incidence of mononuclear cell leukemia in low dose male rats was significantly greater than that in the vehicle controls by life table analysis (vehicle control, 9/50; low dose, 15/50; high dose, 13/50). No effects were observed in female rats (vehicle control, 6/50; low dose, 7/50; high dose, 7/50).

Eye: Cataracts were observed at an increased incidence in high dose male rats (vehicle control, 25/50, 50%; low dose, 19/50, 38%; high dose, 36/50, 72%). The following incidences were observed in females: vehicle control, 17/50 (34%); low dose, 13/50 (26%); high dose, 22/50 (44%). The incidences were not clearly related to cage placement.

Cerebellum: Focal mineralization in the granular layer of the cerebellum was present in 12/49 (24%) high dose male rats but not in any of the other groups of males or females. The mineralization was characterized by multiple spherical basophilic concretions up to 1 mm in diameter. The concretions tended to occur in clusters in the granular layer. No association between the presence of concretions and cell damage was found, nor did the concretions appear to be associated with vessels.

Liver: Neoplastic nodules in male rats occurred with a significant negative trend (vehicle control, 3/50; low dose, 0/50; high dose, 0/50; $P = 0.022$). The incidences of neoplastic nodules in female rats were comparable among groups (vehicle control, 0/50; low dose, 0/50; high dose, 1/50).

TABLE 11. INCIDENCES OF FORESTOMACH LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Hyperkeratosis	0/50	1/50	8/50
Hyperplasia	8/50	16/50	32/50
Squamous cell papilloma	0/50	1/50	3/50
Squamous cell carcinoma	0/50	0/50	3/50
	Vehicle Control	**50 mg/kg**	**100 mg/kg**
FEMALE			
Hyperplasia	4/50	2/50	14/48
Squamous cell papilloma	0/50	0/50	1/48
Squamous cell carcinoma	0/50	0/50	1/48

TABLE 12. ANALYSIS OF FORESTOMACH TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE

	Vehicle Control	100 mg/kg	200 mg/kg
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	3.3%	10.8%
Terminal Rates	0/39 (0%)	1/30 (3%)	2/26 (8%)
Life Table Tests	P=0.032	P=0.448	P=0.067
Incidental Tumor Tests	P=0.052	P=0.448	P=0.115
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	10.1%
Terminal Rates	0/39 (0%)	0/30 (0%)	1/26 (4%)
Life Table Tests	P=0.023	(a)	P=0.074
Incidental Tumor Tests	P=0.066	(a)	P=0.196
Squamous Cell Papilloma or Carcinoma (b)			
Overall Rates	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates	0.0%	3.3%	20.0%
Terminal Rates	0/39 (0%)	1/30 (3%)	3/26 (12%)
Life Table Tests	P=0.002	P=0.448	P=0.006
Incidental Tumor Tests	P=0.006	P=0.448	P=0.025

(a) No P value is presented because no tumors were observed in 100 mg/kg and vehicle control groups.
(b) Historical incidence at this laboratory: 0/147; historical incidence in NTP studies: 6/1,114, 0.5%

SINGLE-ADMINISTRATION STUDIES

All the mice of each sex that received 4,640 or 6,810 mg/kg and all the female mice and 4/5 male mice that received 3,160 mg/kg were dead by day 2 (Table 13). The LD_{50} value as determined by the Spearman-Karber method (Finney, 1978) was 2,815 mg/kg (95% confidence limits of 2,420-3,273 mg/kg) for male mice. The steep survival curve precluded an accurate LD_{50} determination for the females. Animals dosed at 2,150, 3,160, 4,640, or 6,810 mg/kg were inactive and prostrate and had shallow breathing for 2 days after being dosed. On gross necropsy, 2/10 high dose male mice had white opaque eyes; no other dose-related lesions were reported. Based on these findings, the high dose for the 15-day studies was set at 3,000 mg/kg.

TABLE 13. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

Dose (mg/kg)	Survival (b)
MALE	
1,470	5/5
2,150	5/5
3,160	(c) 1/5
4,640	(d) 0/5
6,810	(e) 0/5
FEMALE	
1,470	5/5
2,150	5/5
3,160	(e) 0/5
4,640	(f) 0/5
6,810	(e) 0/5

(a) The initial mean body weight of each male group was 24 g and that of each female group was 18 g. Final body weights were not recorded.
(b) Number surviving/number initially in the group
(c) All deaths occurred on day 2.
(d) Day of death: 1, 1, 1, 2, 2
(e) All deaths occurred on day 1.
(f) Day of death: 1, 1, 1, 1, 2

FIFTEEN-DAY REPEATED-ADMINISTRATION STUDIES

All the mice that received 2,000 or 3,000 mg/kg were dead by day 9 (Table 14). No other compound-related deaths occurred. Mice that received 1,000 mg/kg or more were inactive. At necropsy, irregular thickening of the squamous region of the stomach was observed in 5/5 males and 4/5 females that received 1,000 mg/kg. Slight irregular thickening or irregular nodules were observed in the squamous portion of the stomach of two females and one male that received 500 mg/kg. Dose-related lesions were seen in the stomach of male and female mice after microscopic examination (Table 15). Based on the mortality data, the high dose for the 13-week studies was set at 1,500 mg/kg.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	27	27	0	--
250	5/5	27	27	0	100
500	5/5	27	25	−2	92.6
1,000	5/5	27	21	−6	77.8
2,000	(c) 0/5	27	(d)	(d)	(d)
3,000	(e) 0/5	27	(d)	(d)	(d)
FEMALE					
0	5/5	21	21	0	--
250	(f) 4/5	21	21	0	100
500	5/5	21	20	−1	95.2
1,000	5/5	21	17	−4	81.0
2,000	(g) 0/5	21	(d)	(d)	(d)
3,000	(h) 0/5	21	(d)	(d)	(d)

(a) Number surviving/number initially in the group
(b) Mean weight change of the group
(c) Day of death: 3, 4, 4, 6, 7
(d) No data are presented due to the 100% mortality in this group.
(e) Day of death: 1, 1, 2, 2, 2
(f) Day of death: 7
(g) Day of death: 2, 4, 4, 4, 9
(h) All deaths occurred on day 2.

TABLE 15. INCIDENCES OF NONNEOPLASTIC LESIONS IN THE STOMACHS OF MICE IN THE FIFTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Lesion	0	250 mg/kg	500 mg/kg	1,000 mg/kg	2,000 mg/kg	3,000 mg/kg
MALE						
Epithelial ulceration	--	--	--	1	4	--
Gastritis, acute/chronic, hyperplastic	--	1	5	4	3	--
Squamous atrophy	--	--	--	--	1	5
Gastropathy, hyperplastic	--	--	--	1	1	--
Hyperkeratosis	1	1	--	--	--	--
Submucosal abscess	--	1	--	--	--	--
Intraepithelial abscess	--	--	--	1	--	--
Massive necrosis	--	--	--	--	1	--
FEMALE						
Epithelial ulceration	--	--	--	1	3	2
Gastritis, acute/chronic, hyperplastic	--	1	5	5	4	1
Squamous atrophy	--	--	--	--	1	2
Gastropathy, hyperplastic	--	2	--	--	--	--
Glandular stomach ulceration	--	--	--	--		1

THIRTEEN-WEEK STUDIES

All the mice of each sex that received 750 or 1,500 mg/kg died during the first 4 weeks (Table 16). Two of 10 males and 5/10 females that received 375 mg/kg also died. Mice that received 375 mg/kg or more had tremors and decreased activity. Final weights of surviving dosed and vehicle control mice were comparable. Lung congestion in males and females, cardiac mineralization in males, and hepatocellular vacuolization in females were probably compound related (Table 17). Pulmonary congestion was observed in animals that died during the studies. Testicular atrophy, characterized by hypospermatogenesis with the formation of large giant spermatids and syncytial cells, was seen in male mice at 375, 750, and 1,500 mg/kg.

Dose Selection Rationale: The results from these 13-week studies were used to select doses for the 2-year studies. Decreased survival and toxicity to the lung were seen at 375, 750, and 1,500 mg/kg in male and female mice; these effects were not seen at 190 mg/kg. The maximum dose for the 2-year studies was set at 200 mg/kg.

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Dose (mg/kg)	Survival (b)	Mean Body Weights (a) (grams) Initial	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24	29	+5	--
95	10/10	24	30	+6	103.4
190	10/10	25	31	+6	106.9
375	(d) 8/10	24	28	+4	96.6
750	(e) 0/10	25	(f)	(f)	(f)
1,500	(g) 0/10	23	(f)	(f)	(f)
FEMALE					
0	10/10	18	23	+5	--
95	10/10	18	23	+5	100.0
190	10/10	18	22	+4	95.7
375	(h) 5/10	19	24	+5	104.3
750	(i) 0/10	18	(f)	(f)	(f)
1,500	(j) 0/10	18	(f)	(f)	(f)

(a) Only group weights were taken by laboratory; no individual animal weight data are available.
(b) Number surviving/number in group
(c) Mean weight change of the survivors
(d) Week of death: 11, 12
(e) Week of death: 1, 3, 3, 3, 4, 4, 4, 4, 4, 4
(f) No results are reported due to the 100% mortality in this group.
(g) Week of death: 1, 1, 1, 1, 1, 2, 2, 2, 4, 4
(h) Week of death: 5, 10, 11, 12, 12
(i) Week of death: 3, 4, 4, 4, 4, 4, 4, 4, 4, 4
(j) Week of death: 1, 1, 1, 1, 1, 1, 1, 1, 3, 4

TABLE 17. HISTOPATHOLOGIC LESIONS OBSERVED IN MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Dose (mg/kg)	Hepatocellular Vacuolization (a)	Cardiac Mineralization (minimal severity)	Testicular Atrophy	Lung Congestion
MALE				
0	1/10	0/10	0/10	0/10
95	(b) 1/10	0/10	0/10	0/10
190	1/10	9/10	0/10	0/10
375	2/10	3/10	3/10	1/10
(c) 750	2/9	0/10	9/10	7/10
(c) 1,500	1/10	1/10	2/10	7/10
FEMALE				
0	0/10	1/10		0/10
95	0/10	0/10		0/10
190	5/10	1/10		0/10
375	5/10	2/10		4/10
(c) 750	0/9	0/9		7/10
(c) 1,500	2/7	0/10		9/10

(a) Male: diffuse or focal; female: diffuse
(b) Observed by quality assurance pathologist
(c) Most animals in these groups died early.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

After week 28, mean body weights of high dose male mice were 5% to 10% lower than those of the vehicle controls. Mean body weights of dosed and vehicle control female mice were comparable (Table 18 and Figure 3). Results of hemagglutination inhibition assays, complement fixation assays, and ELISA were negative for virus infection at 6, 12, 18, and 24 months (Appendix L, Table L2).

TABLE 18. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Weeks on Study	Vehicle Control		100 mg/kg			200 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	23	50	23	100.0	50	23	100.0	50
1	25	49	25	100.0	49	25	100.0	50
2	26	49	26	100.0	49	26	100.0	50
3	27	49	27	100.0	49	27	100.0	50
4	29	49	28	96.6	49	28	96.6	50
5	30	49	29	96.7	49	29	96.7	50
6	31	49	30	96.8	49	30	96.8	50
7	31	49	31	100.0	49	30	96.8	50
8	31	49	31	100.0	49	31	100.0	50
9	32	49	32	100.0	49	32	100.0	50
10	32	49	32	100.0	49	33	103.1	50
11	33	49	33	100.0	49	33	100.0	50
12	34	49	34	100.0	49	34	100.0	50
13	34	49	34	100.0	49	34	100.0	50
16	36	49	36	100.0	49	36	100.0	50
20	37	49	37	100.0	49	36	97.3	50
24	39	49	39	100.0	49	38	97.4	50
28	40	49	38	95.0	47	38	95.0	50
32	42	49	39	92.9	47	38	90.5	49
36	41	49	39	95.1	47	38	92.7	49
40	43	49	41	95.3	45	40	93.0	48
44	42	49	41	97.6	44	38	90.5	48
48	44	49	42	95.5	44	40	90.9	48
52	44	49	43	97.7	44	40	90.9	48
56	45	49	43	95.6	44	41	91.1	48
60	46	49	44	95.7	44	42	91.3	48
64	46	48	44	95.7	43	42	91.3	47
68	46	47	45	97.8	42	43	93.5	46
72	46	47	45	97.8	42	43	93.5	45
76	46	46	45	97.8	39	44	95.7	44
80	45	44	44	97.8	37	43	95.6	43
84	45	44	44	97.8	37	43	95.6	43
88	45	43	43	95.6	36	42	93.3	42
92	45	43	44	97.8	36	42	93.3	40
96	43	43	42	97.7	35	40	93.0	38
100	41	42	42	102.4	35	40	97.6	36
104	40	42	41	102.5	34	38	95.0	32
FEMALE								
0	19	50	19	100.0	50	19	100.0	50
1	20	50	20	100.0	50	20	100.0	50
2	20	50	21	105.0	50	21	105.0	50
3	22	50	22	100.0	49	22	100.0	50
4	22	50	22	100.0	49	22	100.0	50
5	23	50	23	100.0	49	23	100.0	50
6	24	50	23	95.8	49	24	100.0	50
7	24	50	24	100.0	49	24	100.0	50
8	25	50	24	96.0	49	25	100.0	50
9	25	50	24	96.0	49	25	100.0	50
10	25	50	25	100.0	48	25	100.0	50
11	25	50	25	100.0	48	25	100.0	50
12	26	50	25	96.2	48	26	100.0	50
13	26	50	25	96.2	48	26	100.0	50
16	27	50	27	100.0	48	27	100.0	50
20	28	50	27	96.4	48	28	100.0	50
24	29	50	29	100.0	47	29	100.0	50
28	29	50	29	100.0	47	30	103.4	50
32	31	50	30	96.8	46	31	100.0	50
36	31	50	31	100.0	46	32	103.2	50
40	33	50	32	97.0	46	33	100.0	50
44	33	50	33	100.0	46	33	100.0	50
48	34	50	34	100.0	46	34	100.0	50
52	35	50	35	100.0	45	35	100.0	49
56	36	50	36	100.0	45	36	100.0	48
60	37	50	37	100.0	45	37	100.0	48
64	38	50	38	100.0	45	38	100.0	48
68	39	50	39	100.0	45	39	100.0	47
72	40	50	40	100.0	45	40	100.0	47
76	41	50	41	100.0	45	40	97.6	46
80	39	50	40	102.6	45	40	102.6	46
84	39	49	41	105.1	45	40	102.6	45
88	38	49	39	102.6	43	39	102.6	44
92	38	46	39	102.6	42	38	100.0	42
96	37	43	38	102.7	41	37	100.0	40
100	36	40	38	105.6	38	37	102.8	37
104	37	39	37	100.0	38	36	97.3	35

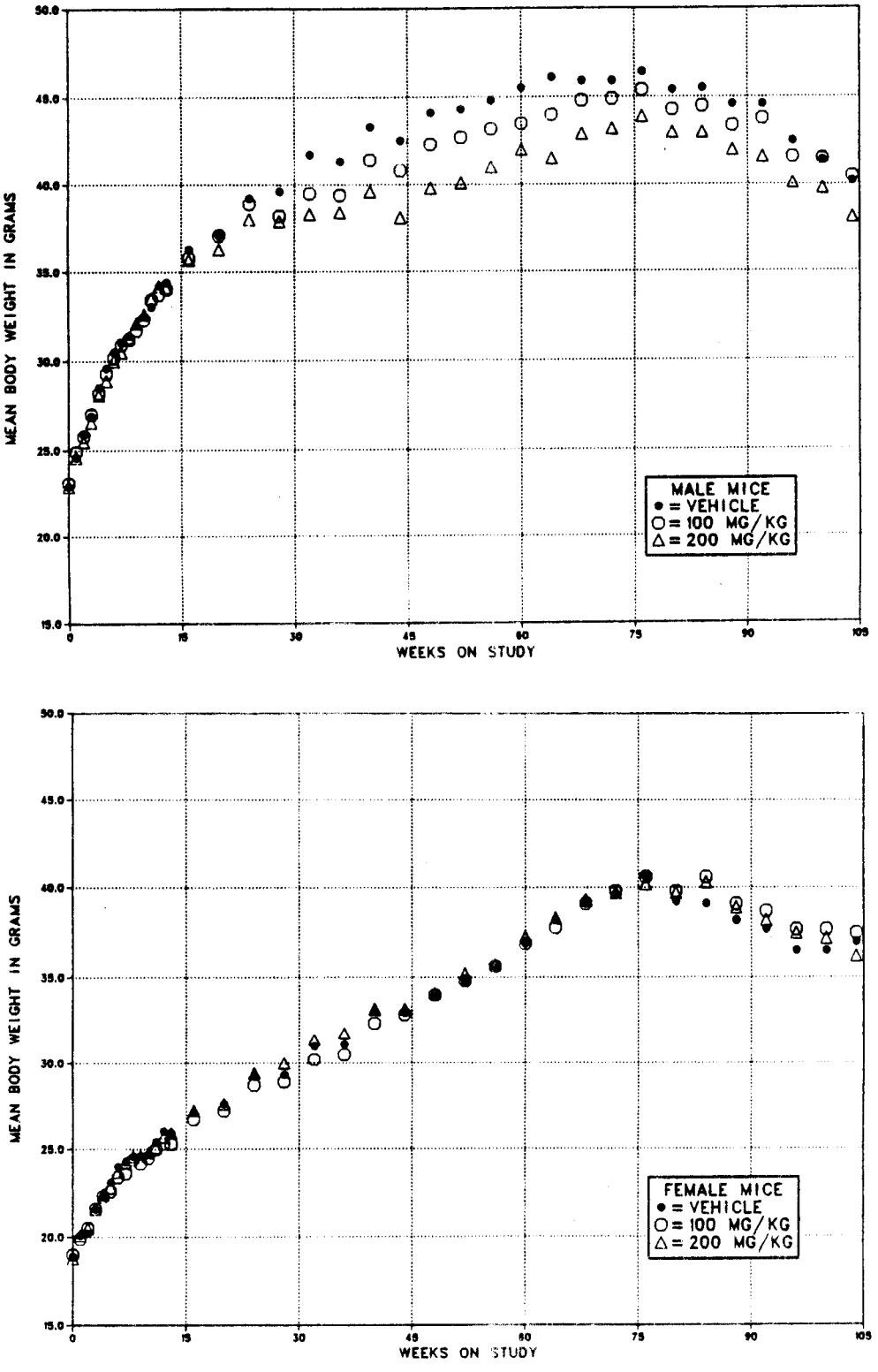


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED DIMETHYL HYDROGEN PHOSPHITE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice administered dimethyl hydrogen phosphite at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. The survival of high dose male mice was significantly lower than that of the vehicle controls (Table 19). No significant differences for survival were seen in dosed female mice.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions in the liver and testis. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); the survival and tumor status for individual male and female mice also are summarized in Appendix B (Tables B3 and B4). Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains 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 19. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	7	8	18
Accidentally killed	1	5	0
Animals missing	0	3	0
Killed at termination	42	33	32
Died during termination period	0	1	0
Survival P values (c)	0.018	0.793	0.029
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	8	15
Accidentally killed	0	3	0
Animals missing	0	1	0
Killed at termination	39	37	34
Died during termination period	0	1	1
Survival P values (c)	0.358	0.772	0.431

(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.

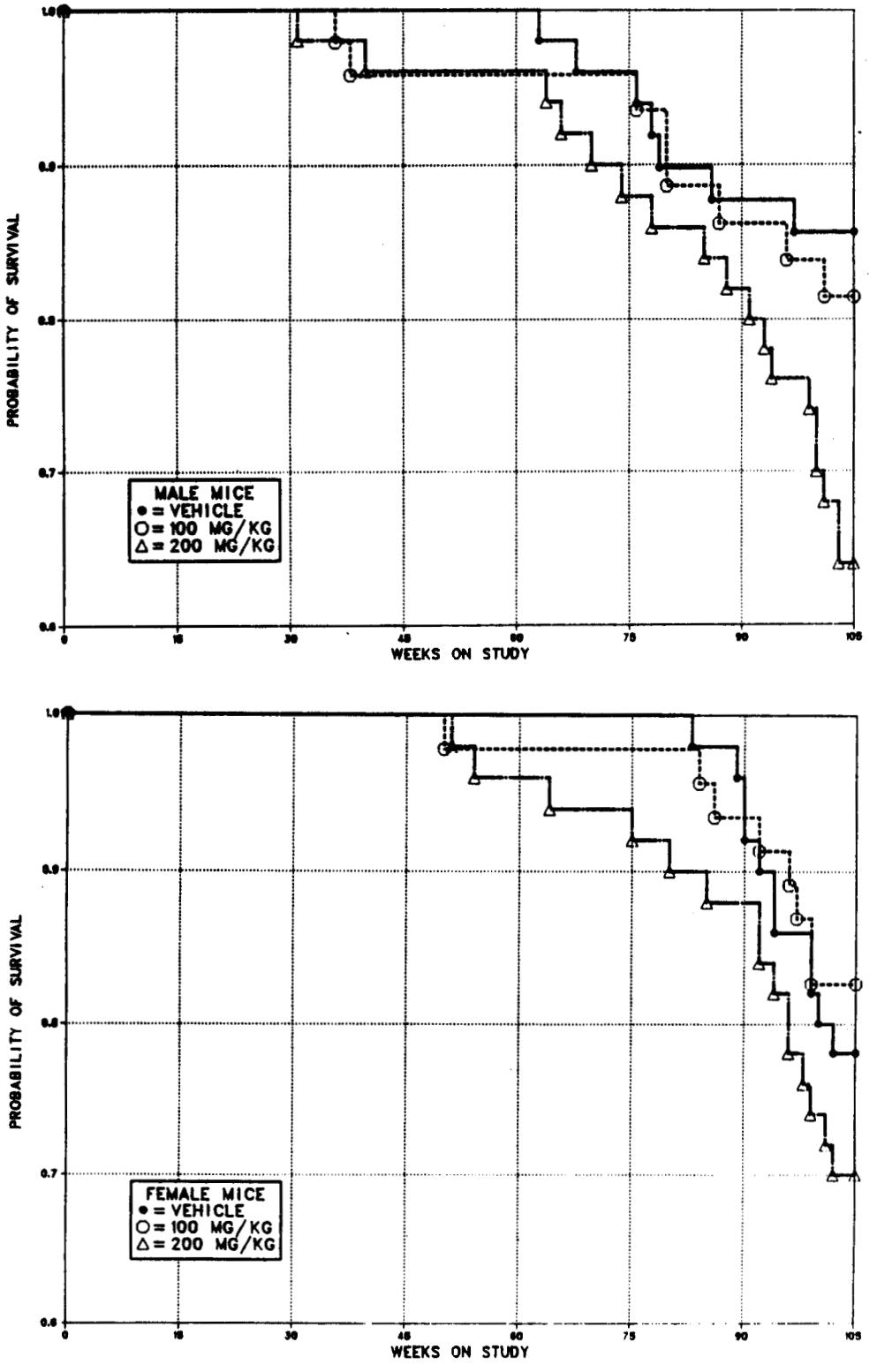


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHYL HYDROGEN PHOSPHITE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Fatty metamorphosis was observed at increased incidences in dosed female mice (vehicle control, 0/50; low dose, 1/49, 2%; high dose, 4/50, 8%). The incidence of hepatocellular adenomas in low dose female mice was significantly greater than that in the vehicle controls (Table 20). Hepatocellular carcinomas were observed in two female vehicle controls but not in any dosed females. The incidence of hepatocellular adenomas or carcinomas (combined) in the low dose female group was not significantly greater than that in the vehicle controls. The incidence of hepatocellular carcinomas in low dose male mice was significantly lower than that in the vehicle controls (vehicle control, 9/50; low dose, 2/47; high dose, 7/50; P=0.038), but the incidence of hepatocellular adenomas or carcinomas (combined) in the low dose group was not significantly different from that of vehicle controls (vehicle control, 19/50; low dose, 10/47; high dose, 13/50).

Testis: Focal calcification was observed at increased incidences in dosed male mice (vehicle control, 2/50, 4%; low dose, 9/47, 19%; high dose, 24/50, 48%). The lesions were more extensive in the dosed animals and appeared as circular-to-oblong deposits that obliterated the underlying cellular features. The shape and location of the deposits suggest mineralization of seminiferous tubules.

TABLE 20. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
Hepatocellular Adenoma (b)			
Overall Rates	0/50 (0%)	6/49 (12%)	3/50 (6%)
Adjusted Rates	0.0%	15.8%	8.6%
Terminal Rates	0/39 (0%)	6/38 (16%)	3/35 (9%)
Life Table Tests	P=0.115	P=0.016	P=0.102
Incidental Tumor Tests	P=0.115	P=0.016	P=0.102
Hepatocellular Adenoma or Carcinoma (c)			
Overall Rates	2/50 (4%)	6/49 (12%)	3/50 (6%)
Adjusted Rates	5.1%	15.8%	8.6%
Terminal Rates	2/39 (5%)	6/38 (16%)	3/35 (9%)
Life Table Tests	P=0.364	P=0.125	P=0.450
Incidental Tumor Tests	P=0.364	P=0.125	P=0.450

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at this laboratory: 4/148, 2.7% ± 2.4%; historical incidence in NTP studies: 47/1,176, 4.0% ± 2.6%
(c) Historical incidence at this laboratory: 7/148, 4.7% ± 3.0%; historical incidence in NTP studies: 80/1,176, 6.8% ± 3.4%

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Dimethyl hydrogen phosphite (DMHP) was administered by gavage in corn oil to male F344/N rats and male and female B6C3F$_1$ mice at doses of 0, 100, or 200 mg/kg and to female F344/N rats at doses of 0, 50, or 100 mg/kg 5 days per week for 103 weeks. The survival of high dose male rats and high dose male mice was lower than that of the vehicle controls; dosed male rats that died during the course of the studies had a greater incidence of pneumonia than did the vehicle control animals that died during the studies. Survival of other groups was comparable to the corresponding vehicle control groups. Mean body weights of high dose male and female rats and high dose male mice were lower than those of the appropriate vehicle control group; other body weights were comparable.

Toxicity and Carcinogenicity in Rats

Dimethyl hydrogen phosphite caused an increased incidence of nonneoplastic and neoplastic lesions of the lung in male and female rats. In high dose male rats, lung neoplasms included squamous cell carcinoma, alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma (Tables 9 and 10). Increased incidences of chronic interstitial pneumonia, adenomatous hyperplasia, alveolar/epithelial hyperplasia, and squamous metaplasia (high dose only) were observed in dosed male rats. All 24 high dose male rats with lung neoplasms also had pneumonia; because pneumonia was widespread in this group (43/50), an association between pneumonia and these lesions could not be determined.

In high dose female rats, a marginal increase in the incidence of alveolar/bronchiolar carcinomas in the lung was observed. This neoplasm was probably related to the administration of DMHP because alveolar/bronchiolar carcinomas were seen in one male and in three female rats receiving 100 mg/kg, suggesting that rats of each sex were probably susceptible to the pulmonary changes. Toxicity to the lung was manifested by increased incidences of interstitial chronic pneumonia, adenomatous hyperplasia, and alveolar epithelium hyperplasia.

The incidence of neoplasms (squamous cell papilloma or squamous cell carcinoma) of the forestomach was increased in the high dose male rats. DMHP also caused hyperplasia and hyperkeratosis of the forestomach in male rats. Dimethyl hydrogen phosphite caused an increased incidence of forestomach hyperplasia in female rats; one squamous cell papilloma and one squamous cell carcinoma were observed in the high dose group.

Dimethyl hydrogen phosphite caused mineralization in the granular layer of the cerebellum in high dose male rats.

Toxicity in Mice

In the 13-week studies, dimethyl hydrogen phosphite caused dose-related lesions of the lung in male and female mice; in contrast to the rat studies, increased incidences of lung neoplasms were not seen in mice after the 2-year dosing period. Compound-related testicular atrophy was seen in male mice in the 13-week studies, and compound-related focal calcification of the testis was seen in male mice in the 2-year studies.

Mutagenicity

Dimethyl hydrogen phosphite was not mutagenic in the *Salmonella typhimurium* assay system with or without metabolic activation and was not mutagenic in *Drosophila melanogaster* (Appendix K, Tables K1 and K2).

Conclusions: Under the conditions of these gavage studies, there was *clear evidence of carcinogenicity** in male F344/N rats receiving dimethyl hydrogen phosphite, as shown by increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and squamous cell carcinomas of the lung and of neoplasms of the forestomach. There was *equivocal evidence of carcinogenicity* in female F344/N rats receiving dimethyl hydrogen phosphite, as shown by marginally increased incidences of alveolar/bronchiolar carcinomas of the lung and of neoplasms of the forestomach. There was *no evidence of carcinogenicity* in male or female B6C3F$_1$ mice receiving dimethyl hydrogen phosphite at doses of 100 or 200 mg/kg for 103 weeks.

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

V. REFERENCES

V. REFERENCES

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APPENDIX A

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

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

	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%)	2 (4%)	1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)		
OSTEOSARCOMA, INVASIVE	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	3 (6%)	1 (2%)	3 (6%)
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(48)	(46)	(47)
C-CELL CARCINOMA, INVASIVE	1 (2%)		
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			5 (10%)
ALVEOLAR/BRONCHIOLAR ADENOMA			5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	20 (40%)
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	9 (18%)	15 (30%)	13 (26%)
#MEDIASTINAL L. NODE	(49)	(47)	(49)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIVE			2 (4%)
#ENDOCARDIUM	(50)	(50)	(50)
NEURILEMOMA, MALIGNANT		1 (2%)	
DIGESTIVE SYSTEM			
*LIP	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	3 (6%)		
#STOMACH	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	3 (6%)
SQUAMOUS CELL CARCINOMA			3 (6%)
KERATOACANTHOMA			1 (2%)
#JEJUNUM	(50)	(49)	(48)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
#URINARY BLADDER	(50)	(48)	(48)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(48)
ADENOMA, NOS	16 (33%)	8 (16%)	14 (29%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	6 (12%)	9 (18%)	3 (6%)
SARCOMA, NOS	1 (2%)		
#THYROID	(50)	(47)	(49)
FOLLICULAR-CELL CARCINOMA	2 (4%)		1 (2%)
C-CELL ADENOMA	2 (4%)	4 (9%)	3 (6%)
C-CELL CARCINOMA	2 (4%)		
#PANCREATIC ISLETS	(49)	(49)	(48)
ISLET-CELL ADENOMA		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	1 (2%)	2 (4%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		2 (4%)
#PROSTATE	(48)	(50)	(49)
OSTEOSARCOMA, INVASIVE			1 (2%)
#TESTIS	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR	42 (84%)	37 (76%)	35 (70%)
MESOTHELIOMA, NOS	4 (8%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
GLIOMA, NOS	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
GLIOMA, NOS	1 (2%)		
*EAR	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*TIBIA	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
UNDIFFERENTIATED CARCINOMA	1 (2%)		
SQUAMOUS CELL CARCINOMA, INVASIVE			1 (2%)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	2 (4%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
PARAGANGLIOMA, NOS		1 (2%)	
SARCOMA, NOS			1 (2%)
*PELVIS	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
C-CELL CARCINOMA, METASTATIC	1 (2%)		
SARCOMA, NOS		1 (2%)	
SARCOMA, NOS, METASTATIC		1 (2%)	
MESOTHELIOMA, NOS	2 (4%)	2 (4%)	1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	13	13
MORIBUND SACRIFICE	6	7	14
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	39	29	23
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1	1	
ANIMAL MISSING			
ANIMAL MISSEXED			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	50	46	49
TOTAL PRIMARY TUMORS	102	92	125
TOTAL ANIMALS WITH BENIGN TUMORS	46	41	42
TOTAL BENIGN TUMORS	72	67	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	20	39
TOTAL MALIGNANT TUMORS	21	21	51
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	2	6
TOTAL SECONDARY TUMORS	4	2	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	7	4	2
TOTAL UNCERTAIN TUMORS	9	4	2
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 HYDROGEN PHOSPHITE

	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			
*SUBCUT TISSUE	(50)	(50)	(50)
NEOPLASM, NOS, UNC PRIM OR META			1 (2%)
TRICHOEPITHELIOMA	1 (2%)		
SARCOMA, NOS			1 (2%)
FIBROMA	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	3 (6%)
SARCOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	6 (12%)	7 (14%)	7 (14%)
CIRCULATORY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)
SARCOMA, NOS, METASTATIC			1 (2%)
#FORESTOMACH	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
NEOPLASM, NOS, METASTATIC			1 (2%)
#URINARY BLADDER	(48)	(50)	(48)
NEOPLASM, NOS, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(50)
ADENOMA, NOS	18 (37%)	17 (35%)	24 (48%)
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	4 (8%)	3 (6%)	5 (10%)
#THYROID	(49)	(49)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
C-CELL ADENOMA	3 (6%)	1 (2%)	4 (9%)
#PANCREATIC ISLETS	(50)	(49)	(48)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RAT IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
NEOPLASM, NOS, UNC PRIM OR META			1 (2%)
SARCOMA, NOS			1 (2%)
FIBROADENOMA	9 (18%)	12 (24%)	14 (28%)
*CLITORAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
ADENOMA, NOS	2 (4%)	2 (4%)	1 (2%)
CYSTADENOMA, NOS		1 (2%)	
#UTERUS	(45)	(48)	(49)
NEOPLASM, NOS, METASTATIC			1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	10 (22%)	10 (21%)	9 (18%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	1 (2%)	
#CERVIX UTERI	(45)	(48)	(49)
LEIOMYOSARCOMA	1 (2%)		
#OVARY	(45)	(48)	(49)
ADENOMA, NOS			1 (2%)
GRANULOSA-CELL TUMOR		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*TIBIA	(50)	(50)	(50)
NEOPLASM, NOS, INVASIVE			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	10	9
MORIBUND SACRIFICE	6	6	8
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	40	33	32
DOSING ACCIDENT			1
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		1	
ANIMAL MISSING			
ANIMAL MISSEXED			

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	36	38	38
TOTAL PRIMARY TUMORS	59	61	78
TOTAL ANIMALS WITH BENIGN TUMORS	32	33	35
TOTAL BENIGN TUMORS	50	48	62
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	11	12
TOTAL MALIGNANT TUMORS	9	11	13
TOTAL ANIMALS WITH SECONDARY TUMORS##			2
TOTAL SECONDARY TUMORS			6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	1
TOTAL UNCERTAIN TUMORS		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			2

* 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 HYDROGEN PHOSPHITE: VEHICLE CONTROL

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 1	1 0 4	1 0 4	0 6 8	1 0 4	0 2 8	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 2	0 9 9	1 0 5	1 0 5	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Squamous cell carcinoma																									
Keratoacanthoma																				X					
Osteosarcoma, invasive								X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																	X						X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive																									
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	X							X				X			X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X							X					
Sarcoma, NOS						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																						X			
C-cell adenoma																							X		
C-cell carcinoma									X																
Parathyroid	–	+	+	+	+	+	+	+	+		+	+	+	+	–	+	+	–	+	+	–	+	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	N	+	+
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																				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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Glioma, NOS	X																								
SPECIAL SENSE ORGANS																									
Eye	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
Ear	+	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	X																								
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
Osteosarcoma							X																		
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
Undifferentiated carcinoma										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
C-cell carcinoma, metastatic																									
Mesothelioma, NOS			X																						
Osteosarcoma, metastatic							X																		
Leukemia, mononuclear cell					X	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	0262	0277	0288	0299	0305	0311	0322	0333	0344	0355	0366	0377	0388	0399	0401	0411	0422	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	105	105	105	099	105	105	071	105	105	105	105	087	105	075	105	105	105	105	041	105	105	105	105	094	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Squamous cell carcinoma												X														1
Keratoacanthoma																										1
Osteosarcoma, invasive																										1
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma									X																	3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	48
C-cell carcinoma, invasive																								X		1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Thymus	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	–	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS			X				X	X					X		X				X	X			X	X		16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma						X									X		X				X					6
Sarcoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma					X																					2
C-cell adenoma																				X						2
C-cell carcinoma																								X		2
Parathyroid	+	–	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	–	–	+	+	+	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	*50
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		42
Mesothelioma, NOS												X							X							4
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												1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Glioma, NOS		X																								1
Ear	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																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	+	N	N	N	N	+	N	+	N	N	N	N	+	N	N	N	N	+	N	*50
Osteosarcoma																										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
Undifferentiated carcinoma																										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
C-cell carcinoma, metastatic																								X		1
Mesothelioma, NOS											X															2
Osteosarcoma, metastatic																										1
Leukemia, mononuclear cell	X								X						X		X									9

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: 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	104	092	082	104	104	096	097	104	054	066	097	104	104	104	057	105	105	105	075	105	105	105	094	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	–	+	–	–	+	+	–	+	+	–	+	–	+	–	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																								X	
DIGESTIVE SYSTEM																									
Oral cavity	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
Squamous cell papilloma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Sarcoma, NOS										X															
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X	X										X		X					X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X						X											X		X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
C-cell adenoma		X			X													X							X
Parathyroid	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	N	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X		X	X	X	X	X			X	X	X	X		X	X			X	X	X		X	X
Mesothelioma, NOS															X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Ear	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																X									
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
Alveolar/bronchiolar ca, metastatic																								X	
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
Paraganglioma, 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
Sarcoma, NOS																									
Sarcoma, NOS, metastatic										X															
Mesothelioma, NOS																			X						
Leukemia, mononuclear cell		X				X	X				X						X	X						X

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
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: 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	084	105	105	105	104	105	054	105	066	105	105	061	105	044	045	105	052	081	101	105	057	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma	X									X																2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										1
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell papilloma	X																									1
Salivary gland	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Sarcoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X	X																				8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X				X							X							X	X				9
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	47
C-cell adenoma																										4
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	–	+	–	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																							X			2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma				X																			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	37
Mesothelioma, NOS																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Ear	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									X																	2
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
Alveolar/bronchiolar ca, metastatic																										1
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
Paraganglioma, 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
Sarcoma, NOS																				X						1
Sarcoma, NOS, metastatic																										1
Mesothelioma, NOS												X														2
Leukemia, mononuclear cell						X				X		X	X					X	X		X	X				15

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: 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	104	079	104	095	104	104	104	104	092	084	104	094	092	105	099	026	050	099	095	055	089	105	105	100	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X												X	
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma								X	X						X			X							
Alveolar/bronchiolar adenoma				X																				X	X
Alveolar/bronchiolar carcinoma	X		X	X	X	X	X					X		X					X	X					
Osteosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastatic																									
Thymus	+	+	+	+	+	+	+	–	–	+	+	–	+	+	–	–	–	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive															X			X							
DIGESTIVE SYSTEM																									
Oral cavity	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
Squamous cell papilloma																							X		
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma				X																					
Keratoacanthoma			X																						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+
Adenoma, NOS	X	X				X		X			X	X								X					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma									X																
C-cell adenoma																			X	X					
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	N	+	N	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	N
Adenocarcinoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X		X	X	X	X		X	X	X	X			X	X				X	X	X	X	X	X	
Mesothelioma, NOS																									
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, invasive																									
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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
SPECIAL SENSE ORGANS																									
Ear	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						X																			
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
Squamous cell carcinoma, invasive															X										
Alveolar/bronchiolar ca, metastatic																									
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
Sarcoma, NOS																									
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																	X								
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: 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	080	091	101	105	102	105	103	105	101	105	104	082	104	105	079	097	105	091	105	105	063	105	105	105	064	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma													X													3
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																		X								5
Alveolar/bronchiolar adenoma												X		X												5
Alveolar/bronchiolar carcinoma					X						X		X			X	X	X	X			X	X	X		20
Osteosarcoma, metastatic																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar ca, metastatic																						X				1
Thymus	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																										2
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X			X														X			3
Squamous cell carcinoma							X				X															3
Keratoacanthoma																										1
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																						X				1
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell papilloma											X															1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS				X			X				X					X	X					X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma													X									X				3
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma																X										3
Parathyroid	–	+	+	+	+	–	–	+	+	+	+	+	–	+	–	–	–	–	+	+	+	+	+	–	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	N	+	+	+	*50
Adenocarcinoma, 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		35
Mesothelioma, NOS											X															1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, invasive																									X	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		X													2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS													X													1
SPECIAL SENSE ORGANS																										
Ear	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																										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
Squamous cell carcinoma, invasive											X															1
Alveolar/bronchiolar ca, metastatic					X																					2
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
Sarcoma, NOS												X														1
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																										1
Leukemia, mononuclear cell	X	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 HYDROGEN PHOSPHITE: VEHICLE CONTROL

ANIMAL NUMBER	091	092	093	094	095	096	097	098	099	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	094	086	104	104	104	104	104	104	104	105	105	105	101	105	105	105	105	083	103	089	106	106
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma								X																	
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X		X				X								X	X			X	X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X																					
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																X									
C-cell adenoma												X					X								
Parathyroid	+	–	–	+	–	+	+	+	–	+	–	+	+	–	–	+	–	+	+	+	+	+	–	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			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	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Leiomyosarcoma																X									
Endometrial stromal polyp														X										X	
Endometrial stromal sarcoma																									
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
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	105	075	091	085	105	090	105	105	105	105	105	105	105	105	105	105	105	081	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																										1
Fibroma												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+		44
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	–	–	–	+	+	+	+		41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Thymus	+	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+		41
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		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+		49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma, NOS	X	X		X					X	X						X			X		X	X	X			18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma							X		X										X							4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Follicular cell adenoma																										1
C-cell adenoma		X																								3
Parathyroid	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	–	+	+	–	+	+	–	+	–	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Islet cell adenoma			X																							1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+		*50
Fibroadenoma												X		X		X					X			X		9
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
Adenoma, NOS	X																									2
Uterus	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Adenocarcinoma, NOS							X																			1
Leiomyosarcoma																										1
Endometrial stromal polyp			X						X		X	X	X						X	X				X		10
Endometrial stromal sarcoma																						X				1
Ovary	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+		49
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																		6

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: 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	095	104	104	094	104	104	104	104	104	104	092	105	105	105	105	104	105	105	105	105	105	056	105	030	094	105
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																										
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Oral cavity	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	
Squamous cell papilloma																								X		
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS								X	X		X		X			X			X		X		X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma								X						X												
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-cell adenoma			X																							
Parathyroid	+	–	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	–	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	
Fibroadenoma			X			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				X													X									
Cystadenoma, NOS																										
Uterus	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endometrial stromal polyp	X			X		X	X								X				X							X
Endometrial stromal sarcoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granulosa cell tumor																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Glioma, 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	
Leukemia, mononuclear cell													X			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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 01	03 11	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 01	04 11	04 12	04 13	04 14	04 15	04 16	04 17	04 18	04 19	05 01	TOTAL
WEEKS ON STUDY	05	14	22	05	05	05	83	01	99	05	68	05	21	05	05	05	95	05	69	05	05	94	05	05	96	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
Alveolar/bronchiolar carcinoma																X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+		45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–		44
Thymus	+	+	–	+	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	–	+	–		40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell papilloma																										1
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		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+		47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+		50
Hemangiosarcoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma, NOS			X	X					X		X					X		X				X		X		17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma					X																					3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell adenoma																										1
Parathyroid	+	+	+	+	–	+	+	+	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+		39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Fibroadenoma													X			X	X							X		12
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
Adenoma, NOS																										2
Cystadenoma, NOS									X																	1
Uterus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+		48
Endometrial stromal polyp								X					X											X		10
Endometrial stromal sarcoma							X																			1
Ovary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+		48
Granulosa cell tumor																		X					X			2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Glioma, 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		*50
Leukemia, mononuclear cell										X												X				7

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	104	104	104	092	104	104	094	097	104	104	105	105	075	105	105	084	103	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, unc prim or metastatic																			X						
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma		X														X									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+
Thymus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule			X																						
Sarcoma, NOS, 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																			X						
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X				X		X	X	X			X			X	X		X	X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X							X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Follicular cell adenoma								X																	
C-cell adenoma							X												X						
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	–	–	–	+	+	+	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Islet cell adenoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, unc prim or metastatic																			X						
Sarcoma, NOS																									
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
Squamous cell papilloma							X																		
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																			X						
Endometrial stromal polyp		X							X						X	X			X		X	X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
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
Neoplasm, NOS, invasive																			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
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 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	053	087	105	102	105	104	104	085	105	105	098	092	105	065	105	076	105	105	105	105	105	092	105	075	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Neoplasm, NOS, unc prim or metastatic																										1
Sarcoma, NOS								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma					X																					3
Sarcoma, NOS, metastatic								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	-	+	-	+	+	+	+	-	+	+	-	+	+	-	+	-	-	+	+	+	+	+	40
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Sarcoma, NOS, 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	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma											X															1
Squamous cell carcinoma																										1
Small intestine	A	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	A	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplasm, NOS, metastatic																										1
Urinary bladder	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplasm, NOS, metastatic																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X			X	X	X				X	X				X	X		X	X		X	X	24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X			X				X																	5
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
Follicular cell adenoma																										1
C-cell adenoma																	X								X	4
Parathyroid	A	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	34
Pancreatic islets	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Neoplasm, NOS, unc prim or metastatic																										1
Sarcoma, NOS												X														1
Fibroadenoma						X	X	X	X			X					X	X	X							14
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
Squamous cell papilloma																										1
Adenoma, NOS									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
Neoplasm, NOS, metastatic																										1
Endometrial stromal polyp													X				X									9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
Adenoma, NOS						X																				1
NERVOUS SYSTEM																										
Brain	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	N	N	N	N	N	+	N	N	N	+	N	N	N	+	N	N	N	N	N	+	N	+	N	*50
Neoplasm, NOS, invasive																										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				7

*Animals Necropsied

APPENDIX B

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

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

	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)
SQUAMOUS CELL CARCINOMA		1 (2%)	
BASAL-CELL TUMOR		1 (2%)	
FIBROMA			1 (2%)
*SUBCUT TISSUE	(50)	(47)	(50)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		1 (2%)	
RHABDOMYOSARCOMA	1 (2%)		2 (4%)
NEURILEMOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(47)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	2 (4%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (12%)	5 (11%)	8 (16%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		2 (4%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
MAST-CELL LEUKEMIA	1 (2%)		
GRANULOCYTIC SARCOMA		1 (2%)	
#LIVER	(50)	(47)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(47)	(49)
HEMANGIOSARCOMA	1 (2%)		
ANGIOSARCOMA		1 (2%)	
#MESENTERIC L. NODE	(27)	(26)	(25)
ANGIOSARCOMA		1 (4%)	
*ADIPOSE TISSUE	(50)	(47)	(50)
HEMANGIOMA		1 (2%)	
#LIVER	(50)	(47)	(50)
HEMANGIOSARCOMA			4 (8%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(47)	(50)
HEPATOCELLULAR ADENOMA	12 (24%)	8 (17%)	8 (16%)
HEPATOCELLULAR CARCINOMA	9 (18%)	2 (4%)	7 (14%)
#FORESTOMACH	(50)	(45)	(47)
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(47)	(50)
TUBULAR-CELL ADENOMA	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(45)	(48)
ADENOMA, NOS		2 (4%)	1 (2%)
#ADRENAL	(50)	(46)	(49)
CORTICAL ADENOMA	3 (6%)		
#THYROID	(44)	(45)	(49)
FOLLICULAR-CELL ADENOMA	3 (7%)		1 (2%)
#PANCREATIC ISLETS	(50)	(47)	(49)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(47)	(50)
PAPILLOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(47)	(49)
SARCOMA, NOS		1 (2%)	
#BRAIN	(50)	(47)	(49)
GRANULAR-CELL TUMOR, MALIGNANT	1 (2%)		
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(47)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(47)	(50)
GRANULAR-CELL TUMOR, INVASIVE	1 (2%)		
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(47)	(50)
FIBROSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	6	4	14
MORIBUND SACRIFICE	1	5	4
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	42	33	32
DOSING ACCIDENT	1		
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		5	
ANIMAL MISSING		3	
ANIMAL MISSEXED			

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	34	21	31
TOTAL PRIMARY TUMORS	51	33	43
TOTAL ANIMALS WITH BENIGN TUMORS	22	12	14
TOTAL BENIGN TUMORS	27	17	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	12	22
TOTAL MALIGNANT TUMORS	24	16	27
TOTAL ANIMALS WITH SECONDARY TUMORS##	3		
TOTAL SECONDARY TUMORS	3		
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 B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
FIBROSARCOMA		2 (4%)	
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
RHABDOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)		
SARCOMA, NOS, METASTATIC			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	3 (6%)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	6 (12%)	5 (10%)	6 (12%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	5 (10%)	3 (6%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)	1 (2%)	
PLASMA-CELL MYELOMA		1 (2%)	
UNDIFFERENTIATED LEUKEMIA	2 (4%)		3 (6%)
*ABDOMINAL CAVITY	(50)	(49)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#SPLEEN	(50)	(48)	(48)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#MANDIBULAR L. NODE	(39)	(37)	(33)
SARCOMA, NOS, METASTATIC			1 (3%)
#LUMBAR LYMPH NODE	(39)	(37)	(33)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
#MESENTERIC L. NODE	(39)	(37)	(33)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
#THYMUS	(44)	(38)	(45)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)		
HEMANGIOSARCOMA, UNC PRIM OR MET			1 (2%)
#SPLEEN	(50)	(48)	(48)
HEMANGIOSARCOMA, UNC PRIM OR MET			1 (2%)
#LIVER	(50)	(49)	(50)
ANGIOSARCOMA		1 (2%)	
#UTERUS	(49)	(49)	(49)
HEMANGIOMA			1 (2%)
#OVARY	(47)	(48)	(49)
HEMANGIOMA	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA		6 (12%)	3 (6%)
HEPATOCELLULAR CARCINOMA	2 (4%)		
#JEJUNUM	(47)	(49)	(45)
LEIOMYOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(45)	(48)
ADENOMA, NOS	12 (26%)	9 (20%)	10 (21%)
CHROMOPHOBE ADENOMA	1 (2%)		1 (2%)
#ADRENAL	(49)	(45)	(47)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
#THYROID	(47)	(48)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	1 (2%)		
#UTERUS	(49)	(49)	(49)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA			1 (2%)
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(47)	(48)	(49)
PAPILLARY CYSTADENOMA, NOS	2 (4%)		
GRANULOSA-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*VERTEBRA	(50)	(49)	(50)
OSTEOSARCOMA	1 (2%)		
*LUMBAR VERTEBRA	(50)	(49)	(50)
FIBROSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(50)
LIPOMA			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
FIBROSARCOMA			1 (2%)
HEAD			
SARCOMA, NOS			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	8	4	13
MORIBUND SACRIFICE	3	5	3
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	39	37	34
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		3	
ANIMAL MISSING		1	
ANIMAL MISSEXED			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	37	30	32
TOTAL PRIMARY TUMORS	49	39	45
TOTAL ANIMALS WITH BENIGN TUMORS	20	18	16
TOTAL BENIGN TUMORS	21	22	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	15	23
TOTAL MALIGNANT TUMORS	27	17	24
TOTAL ANIMALS WITH SECONDARY TUMORS##	2		1
TOTAL SECONDARY TUMORS	2		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			2

* 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 HYDROGEN PHOSPHITE: VEHICLE CONTROL

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 6 3	0 0 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 6 8	1 0 5	1 0 5	0 9 7	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																					X				
Alveolar/bronchiolar adenoma											X										X	X			
Alveolar/bronchiolar carcinoma															X		X								X
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymph nodes	–	+	+	–	+	+	–	–	+	–	+	+	–	–	–	–	+	–	–	–	+	+	–	–	+
Thymus	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X		X	X						X			X							X
Hepatocellular carcinoma												X									X				X
Malig. lymphoma, histiocytic type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma			X																						
Thyroid	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma							X								X										
Parathyroid	–	–	+	–	–	–	–	+	+	–	–	–	+	–	–	+	+	–	–	+	–	–	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	–
Penis	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
Papilloma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, malignant			X																						
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
Granular cell tumor, invasive			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
Malig. lymphoma, lymphocytic type											X														
Malig. lymphoma, histiocytic type					X																				
Undifferentiated leukemia																						X			
Mast cell leukemia																									

+ : 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
WEEKS ON STUDY	105	076	105	105	105	105	105	105	078	105	079	105	105	105	105	105	105	105	105	086	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Rhabdomyosarcoma		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																							X			2
Alveolar/bronchiolar adenoma							X			X		X														6
Alveolar/bronchiolar carcinoma									X				X						X							6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph nodes	–	+	+	+	–	+	+	+	+	–	+	–	–	–	+	+	–	+	+	–	+	+	–	+	+	27
Thymus	+	–	–	+	+	–	+	+	–	–	–	+	+	–	+	–	+	+	+	–	–	+	+	+	–	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X					X	X										X			X				X	12
Hepatocellular carcinoma				X								X		X							X	X	X			9
Malig. lymphoma, histiocytic type															X											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	N	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma	X																									1
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma							X												X							3
Thyroid	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	44
Follicular cell adenoma															X											3
Parathyroid	+	–	+	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	+	15
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Penis	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
Papilloma, NOS							X																			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, malignant																										1
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	*50
Granular cell tumor, invasive																										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
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type																										1
Undifferentiated leukemia																										1
Mast cell leukemia	X																									1

* Animals Necropsied

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

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	1 0 5	0 7 6	0 7 6	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 4 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 1	1 0 5	1 0 5	0 7 6	1 0 5	1 0 2 7	1 0 5	0 0 1	1 0 5
INTEGUMENTARY SYSTEM																								
Skin	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Squamous cell carcinoma																								
Basal cell tumor														X										
Subcutaneous tissue	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Fibrosarcoma																				X				
Neurilemoma, malignant																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Alveolar/bronchiolar adenoma				X																				
Alveolar/bronchiolar carcinoma	X													X	X									X
Trachea	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Angiosarcoma																	X							
Lymph nodes	+	M	M	+	–	+	+	+	+	–	+	–	+	–	+	–	–	+	–	+	–	–	+	M	–
Angiosarcoma								X																
Thymus	+	M	M	+	+	+	–	–	+	–	+	–	+	+	+	+	–	–	+	–	+	+	M	–
CIRCULATORY SYSTEM																								
Heart	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
DIGESTIVE SYSTEM																								
Salivary gland	+	M	M	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	M	+
Liver	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Hepatocellular adenoma							X						X			X								X
Hepatocellular carcinoma	X																							
Bile duct	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Gallbladder & common bile duct	N	M	M	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	M	+
Pancreas	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Esophagus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Stomach	+	M	M	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Papilloma, NOS																								
Small intestine	+	M	M	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	–	M	+
Large intestine	+	M	M	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	M	+
URINARY SYSTEM																								
Kidney	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Urinary bladder	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	M	+
ENDOCRINE SYSTEM																								
Pituitary	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma, NOS																X								
Adrenal	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	M	+
Thyroid	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Parathyroid	–	M	M	+	+	+	+	–	+	–	+	–	+	–	+	+	–	–	–	–	–	–	M	+
Pancreatic islets	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Islet cell adenoma																								X
REPRODUCTIVE SYSTEM																								
Mammary gland	N	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N
Testis	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Prostate	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	M	+
NERVOUS SYSTEM																								
Brain	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Sarcoma, NOS														X										
ALL OTHER SYSTEMS																								
Multiple organs NOS	N	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N
Mesothelioma, malignant								X																
Malignant lymphoma, NOS																								
Granulocytic sarcoma																								
Adipose tissue		M	M																				M	
Hemangioma																								

+ : 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: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	1005	1005	0805	1005	1005	0857	0665	1005	0336	1005	0227	0338	0801	1005	1005	1005	1005	1005	1005	1005	1005	1005	0682	0996	1050	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*47
Squamous cell carcinoma			X																							1
Basal cell tumor																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*47
Fibrosarcoma																										1
Neurilemoma, malignant																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma																X										2
Alveolar/bronchiolar carcinoma					X																					5
Trachea	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Angiosarcoma																										1
Lymph nodes	–	+	+	+	–	+	–	–	–	–	+	+	+	+	+	–	–	+	–	–	–	+	+	+	+	26
Angiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma								X								X				X					X	8
Hepatocellular carcinoma						X																				2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	*47
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Papilloma, NOS																									X	1
Small intestine	+	+	+	+	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	45
Adenoma, NOS														X												2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	+	–	–	–	–	+	+	–	–	+	–	–	–	+	–	–	–	–	–	+	+	+	+	–	+	21
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma																X										2
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		*47
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, 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	*47
Mesothelioma, malignant																										1
Malignant lymphoma, NOS																	X									1
Granulocytic sarcoma			X																							1
Adipose tissue																										
Hemangioma																X										1

*Animals Necropsied

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

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	064	105	105	066	105	105	031	078	105	105	100	094	105	105	105	105	103	105	105	105	105	105	040	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS													X												
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma	X																	X		X	X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Lymph nodes	+	–	–	+	+	–	–	+	+	+	–	+	–	–	+	+	–	–	+	–	–	–	+	A	+
Thymus	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	A	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X			X		X			X						X
Hepatocellular carcinoma																					X				
Hemangiosarcoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Squamous cell carcinoma					X																				
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	A	+
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Follicular cell adenoma			X																						
Parathyroid	+	+	–	–	–	+	+	–	+	–	+	–	+	+	+	+	+	–	–	+	–	–	–	A	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Islet cell adenoma																									
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	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, 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
Fibrosarcoma													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
Malig. lymphoma, histiocytic 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: 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	105	105	105	088	105	105	105	085	105	105	101	105	099	105	105	105	070	105	103	074	093	091	105	101	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																					X					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Rhabdomyosarcoma					X																X					2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X		X																			3
Alveolar/bronchiolar carcinoma		X											X	X											X	8
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	–	+	+	–	–	+	–	+	–	–	–	–	+	–	+	+	+	–	+	+	–	+	–	–	25
Thymus	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	–	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X		X			X											8
Hepatocellular carcinoma					X							X			X	X					X	X				7
Hemangiosarcoma									X											X					X	4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+		47
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS											X															1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Parathyroid	–	–	+	+	–	–	–	+	+	+	–	+	+	+	–	–	+	+	+	–	–	–	+	–	+	26
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma											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	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								1
Adenocarcinoma, 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
Fibrosarcoma																										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
Malig. lymphoma, histiocytic type	X																									2

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: 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	105	105	105	090	099	105	105	089	105	105	105	105	105	105	105	105	105	105	105	094	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+
Fibrous histiocytoma, malignant																		X							
Hemangiosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar carcinoma																X									
Osteosarcoma, metastatic																									
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	+	–	+	+	–	–	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Malig. lymphoma, lymphocytic type					X																				
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adenoma, NOS										X		X				X		X							
Chromophobe adenoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Cortical adenoma			X																						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	–	–	–	–	–	+	–	–	+	–	–	–	+	–	–	–	+	–	–	–	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Papillary cystadenoma, NOS																		X					X		
Granulosa cell tumor																									
Hemangioma																									
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
Fibrosarcoma																							X		
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
Malignant lymphoma, NOS						X		X					X												
Malig. lymphoma, lymphocytic type														X											
Malig. lymphoma, histiocytic type																							X		
Malignant lymphoma, mixed type																									
Undifferentiated leukemia							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 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
WEEKS ON STUDY	105	105	105	105	105	092	090	083	105	100	105	105	105	105	105	099	095	094	105	105	105	102	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Fibrous histiocytoma, malignant																										1
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic			X																							1
Alveolar/bronchiolar adenoma																						X				2
Alveolar/bronchiolar carcinoma																	X									2
Osteosarcoma, metastatic																X										1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	–	+	–	+	+	+	+	+	39
Thymus	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	44
Malig. lymphoma, lymphocytic type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X											X												2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Esophagus	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	46
Adenoma, NOS				X					X	X		X	X			X			X					X		12
Chromophobe adenoma							X																			1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	47
Follicular cell adenoma						X																				1
Parathyroid	–	–	+	–	+	–	–	+	–	–	–	+	–	–	–	–	–	+	+	–	+	–	+	+	+	15
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	*50
Fibroadenoma									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Leiomyosarcoma																										1
Ovary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Papillary cystadenoma, NOS																										2
Granulosa cell tumor																								X		1
Hemangioma			X																•							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Fibrosarcoma																										1
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
Malignant lymphoma, NOS																						X				1
Malig. lymphoma, lymphocytic type			X						X										X							6
Malig. lymphoma, histiocytic type		X									X							X								5
Malignant lymphoma, mixed type				X	X	X																				3
Undifferentiated leukemia																										2

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: LOW 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	105	105	097	105	105	105	084	105	105	105	105	099	050	105	105	105	003	105	105	105	105	105	092	096	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Fibrosarcoma																								X	
Rhabdomyosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	–	+	+	–	+	+
Malig. lymphoma, histiocytic type																									
Thymus	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	–	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma	X																			X					
Angiosarcoma										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																							X		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+
Adenoma, NOS						X		X			X	X							X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	–	+	–	+	+	–	+	+	–	–	–	+	–	–	+	–	–	+	–	–	–	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	N	+
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp												X													
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
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS										X															
Malig. lymphoma, lymphocytic type				X	X																	X			
Malig. lymphoma, histiocytic type														X					X						
Malignant lymphoma, mixed type																									
Plasma cell myeloma																									

+ : 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: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	0009	1005	0211	0869	0030	1005	1005	1005	1005	1005	0999	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma				X																						2
Rhabdomyosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma					X													X			X					3
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	–	+	M	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	–	–	+	37
Malig. lymphoma, histiocytic type															X											1
Thymus	+	+	M	–	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	–	–	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	M	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma								X								X	X			X						6
Angiosarcoma																										1
Bile duct	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	M	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Large intestine	+	+	M	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS												X	X			X					X					9
Adrenal	+	+	M	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	45
Cortical adenoma															X											1
Thyroid	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Parathyroid	+	–	M	–	+	–	–	–	+	–	–	+	–	–	+	+	–	–	–	–	–	+	–	–	+	18
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	M	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS																X										1
Uterus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																										1
Ovary	+	+	M	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	M	N	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
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, NOS																										1
Malig. lymphoma, lymphocytic type								X													X					5
Malig. lymphoma, histiocytic type																									X	3
Malignant lymphoma, mixed type												X														1
Plasma cell myeloma											X															1

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE: HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	099	105	105	064	105	101	105	102	105	105	105	105	105	105	085	095	105	105	105	105	095	051	105	105	C
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma, unc prim or meta																									
RESPIRATORY SYSTEM																									
and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma														X											
Sarcoma, NOS, metastatic							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma, unc prim or meta																									
Malig. lymphoma, histiocytic type			X																						
Lymph nodes	–	+	+	+	+	+	+	–	–	+	–	–	–	–	+	–	+	+	+	–	–	+	+	+	
Sarcoma, NOS, metastatic							X																		
Malig. lymphoma, histiocytic type																									
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	
Malig. lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	
Adenoma, NOS							X			X	X							X		X		X		X	
Chromophobe adenoma																									
Adrenal	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	
Follicular cell adenoma			X			X																			
Parathyroid	+	–	–	–	–	+	+	–	–	–	+	–	–	+	–	–	–	–	+	–	+	–	–	–	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, NOS	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, NOS										X															
Fibrosarcoma																		X							
Hemangioma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
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
Lipoma																									
Malig. lymphoma, lymphocytic type										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
Fibrosarcoma																									
Malignant lymphoma, NOS																									
Malig. lymphoma, lymphocytic type		X																X							
Malig. lymphoma, histiocytic type																	X								X
Undifferentiated leukemia	X														X							X			
Head NOS																									
Sarcoma, NOS							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: 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	092	105	105	096	105	105	105	075	080	098	105	105	105	105	105	054	094	105	096	105	105	105	092	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	*50
Hemangiosarcoma, unc prim or meta															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma, unc prim or meta															X											1
Malig. lymphoma, histiocytic type																										1
Lymph nodes	+	–	+	–	–	+	+	–	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	33
Sarcoma, NOS, metastatic																										1
Malig. lymphoma, histiocytic type	X																									1
Thymus	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Malig. lymphoma, lymphocytic type																X										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X												X											3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	N	N	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Small intestine	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Adenoma, NOS									X											X		X				10
Chromophobe adenoma											X															1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Follicular cell adenoma																										2
Parathyroid	+	+	–	+	+	–	–	–	–	–	–	–	+	–	–	+	+	–	–	+	+	–	–	–	–	16
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Fibrosarcoma																										1
Hemangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
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	X	N	N	N	*50
Lipoma																										1
Malig. lymphoma, lymphocytic type																										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	X	N	*50
Fibrosarcoma																										1
Malignant lymphoma, NOS						X	X										X									3
Malig. lymphoma, lymphocytic type			X																X	X				X		6
Malig. lymphoma, histiocytic type																						X				3
Undifferentiated leukemia																										3
Head NOS																										
Sarcoma, NOS																										1

* Animals Necropsied

APPENDIX C

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

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

	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)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
FIBROSIS	1 (2%)		
NECROSIS, FAT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
CONGESTION, NOS	1 (2%)		1 (2%)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	7 (14%)	19 (38%)	43 (86%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HYPERPLASIA, ADENOMATOUS		3 (6%)	26 (52%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	7 (14%)	16 (32%)
METAPLASIA, SQUAMOUS			3 (6%)
METAPLASIA, OSSEOUS			1 (2%)
HISTIOCYTOSIS	5 (10%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(49)	(49)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPOPLASIA, NOS	1 (2%)		1 (2%)
MYELOFIBROSIS	2 (4%)		1 (2%)
#SPLEEN	(50)	(50)	(49)
NECROSIS, NOS			1 (2%)
HEMOSIDEROSIS	6 (12%)	4 (8%)	2 (4%)
HEMATOPOIESIS	2 (4%)	1 (2%)	8 (16%)
#MANDIBULAR L. NODE	(49)	(47)	(49)
ANGIECTASIS			1 (2%)
#MEDIASTINAL L. NODE	(49)	(47)	(49)
EDEMA, NOS			1 (2%)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
HEMORRHAGE, CHRONIC		1 (2%)	
#HEPATIC LYMPH NODE	(49)	(47)	(49)
EDEMA, NOS			1 (2%)
#MESENTERIC L. NODE	(49)	(47)	(49)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
NECROSIS, NOS			1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
#ADRENAL	(50)	(50)	(50)
HEMATOPOIESIS			3 (6%)
#THYMUS	(36)	(38)	(39)
CYST, NOS	1 (3%)		
CIRCULATORY SYSTEM			
*MEDIASTINUM	(50)	(50)	(50)
PERIARTERITIS			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
*STERNUM	(50)	(50)	(50)
ANEURYSM	1 (2%)		
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS	35 (70%)	37 (74%)	32 (64%)
DEGENERATION, NOS	2 (4%)	3 (6%)	
#HEART/ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS			2 (4%)
FIBROSIS	1 (2%)		
*MESENTERIC ARTERY	(50)	(50)	(50)
ANEURYSM	1 (2%)		
ARTERIOSCLEROSIS, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#STOMACH	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#KIDNEY	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#URINARY BLADDER	(50)	(48)	(48)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(49)
ATROPHY, NOS	1 (2%)		1 (2%)
#LIVER	(50)	(50)	(50)
CONGENITAL MALFORMATION, NOS	2 (4%)	1 (2%)	3 (6%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)		
DEGENERATION, NOS	1 (2%)	4 (8%)	1 (2%)
NECROSIS, NOS		1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	8 (16%)	13 (26%)	13 (26%)
BASOPHILIC CYTO CHANGE	16 (32%)	13 (26%)	7 (14%)
EOSINOPHILIC CYTO CHANGE	8 (16%)	5 (10%)	4 (8%)
CLEAR-CELL CHANGE	2 (4%)		
ANGIECTASIS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
DEGENERATION, NOS			2 (4%)
NECROSIS, NOS	1 (2%)	1 (2%)	2 (4%)
#LIVER/PERIPORTAL	(50)	(50)	(50)
HYPERTROPHY, NOS			1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	43 (86%)	44 (88%)	44 (88%)
#PANCREAS	(49)	(49)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	1 (2%)	
ATROPHY, NOS	13 (27%)	13 (27%)	13 (27%)
HYPERPLASIA, NODULAR	2 (4%)		1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
ANGIECTASIS		1 (2%)	
#ESOPHAGUS	(48)	(48)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#ESOPHAGEAL ADVENTITIA	(48)	(48)	(50)
HEMOSIDEROSIS		1 (2%)	
#STOMACH	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS		1 (2%)	1 (2%)
ULCER, CHRONIC			1 (2%)
HYPERPLASIA, NOS	8 (16%)	16 (32%)	32 (64%)
HYPERKERATOSIS		1 (2%)	8 (16%)
#LARGE INTESTINE	(49)	(49)	(48)
PARASITISM			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	1 (2%)	2 (4%)	
HYDRONEPHROSIS			1 (2%)
NEPHROPATHY	38 (76%)	34 (68%)	33 (66%)
NEPHROSIS, NOS		1 (2%)	
INFARCT, ACUTE			1 (2%)
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS	8 (16%)	9 (18%)	3 (6%)
INCLUSION, CYTOPLASMIC			2 (4%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
FIBROSIS, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
#URINARY BLADDER	(50)	(48)	(48)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
#U. BLADDER/SEROSA	(50)	(48)	(48)
INFLAMMATION, CHRONIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(48)
CYST, NOS	4 (8%)	5 (10%)	6 (13%)
HEMORRHAGE	1 (2%)		
HEMOSIDEROSIS			1 (2%)
HYPERTROPHY, FOCAL	2 (4%)	2 (4%)	4 (8%)
HYPERPLASIA, FOCAL	9 (19%)	7 (14%)	8 (17%)
ANGIECTASIS	1 (2%)	1 (2%)	1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
#PITUITARY INTERMEDIA	(48)	(50)	(48)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL	(50)	(50)	(50)
LIPOIDOSIS		2 (4%)	1 (2%)
ANGIECTASIS	1 (2%)		2 (4%)
#ADRENAL CORTEX	(50)	(50)	(50)
LIPOIDOSIS	5 (10%)	7 (14%)	8 (16%)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, FOCAL	4 (8%)	1 (2%)	2 (4%)
ANGIECTASIS			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	7 (14%)	3 (6%)	1 (2%)
#THYROID	(50)	(47)	(49)
CYST, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, C-CELL	24 (48%)	27 (57%)	20 (41%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(49)	(49)	(48)
HYPERPLASIA, FOCAL			2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	4 (8%)	2 (4%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		2 (4%)	
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
*PREPUCE	(50)	(50)	(50)
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
#PROSTATE	(48)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	3 (6%)		
INFLAMMATION CHRONIC SUPPURATIVE		1 (2%)	2 (4%)
INFLAMMATION, GRANULOMATOUS	5 (10%)	5 (10%)	2 (4%)
HYPERTROPHY, NOS			1 (2%)
HYPERTROPHY, FOCAL	11 (23%)	15 (30%)	14 (29%)
HYPERTROPHY, DIFFUSE	2 (4%)	1 (2%)	
HYPERPLASIA, FOCAL	4 (8%)	5 (10%)	
#TESTIS	(50)	(49)	(50)
MINERALIZATION		1 (2%)	
INFARCT, ACUTE			1 (2%)
ATROPHY, NOS	8 (16%)	4 (8%)	9 (18%)
HYPERPLASIA, FOCAL	2 (4%)	2 (4%)	
HYPERPLASIA, INTERSTITIAL CELL	6 (12%)	5 (10%)	14 (28%)
*EPIDIDYMIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
*SCROTUM	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
NECROSIS, FAT	2 (4%)		2 (4%)
PIGMENTATION, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
MALACIA		1 (2%)	
#CEREBELLUM	(49)	(50)	(49)
MINERALIZATION			12 (24%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
CATARACT	25 (50%)	19 (38%)	36 (72%)
PHTHISIS BULBI			1 (2%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
DETACHMENT	1 (2%)		
ATROPHY, NOS	19 (38%)	29 (58%)	21 (42%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	3 (6%)	
*PLEURA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*PERICARDIUM	(50)	(50)	(50)
LIPOGRANULOMA	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
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 HYDROGEN PHOSPHITE

	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			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
#LUNG	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	
EDEMA, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
PNEUMONIA, ASPIRATION		1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE		3 (6%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	4 (8%)	5 (10%)	33 (66%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	1 (2%)
FIBROSIS, FOCAL	1 (2%)		
HEMOSIDEROSIS		2 (4%)	1 (2%)
HYPERPLASIA, ADENOMATOUS			10 (20%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		11 (22%)
HISTIOCYTOSIS	4 (8%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(41)	(45)	(49)
HYPOPLASIA, NOS			1 (2%)
OSTEOSCLEROSIS		1 (2%)	3 (6%)
HISTIOCYTOSIS			1 (2%)
MYELOFIBROSIS			1 (2%)
#SPLEEN	(50)	(50)	(49)
HEMOSIDEROSIS	17 (34%)	9 (18%)	13 (27%)
HYPERPLASIA, STROMAL	1 (2%)		
HEMATOPOIESIS	8 (16%)	4 (8%)	7 (14%)
#SPLENIC SEROSA	(50)	(50)	(49)
FIBROSIS			1 (2%)
#MEDIASTINAL L. NODE	(45)	(44)	(40)
HEMORRHAGE		1 (2%)	
#THYMUS	(41)	(40)	(47)
CYST, NOS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(50)
FIBROSIS	17 (34%)	16 (33%)	13 (26%)
DEGENERATION, NOS	5 (10%)	6 (12%)	4 (8%)
#HEART/ATRIUM	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*AORTA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBUS, MURAL			1 (2%)
ARTERIOSCLEROSIS, NOS			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#COLON	(50)	(48)	(46)
PERIARTERITIS	1 (2%)		
#UTERUS	(45)	(48)	(49)
THROMBUS, FIBRIN			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
#SALIVARY GLAND	(50)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#LIVER	(50)	(50)	(50)
CONGENITAL MALFORMATION, NOS	3 (6%)	2 (4%)	4 (8%)
CONGESTION, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	4 (8%)	8 (16%)
INFLAMMATION, GRANULOMATOUS	17 (34%)	8 (16%)	10 (20%)
NECROSIS, NOS		2 (4%)	1 (2%)
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	3 (6%)	3 (6%)	3 (6%)
BASOPHILIC CYTO CHANGE	36 (72%)	28 (56%)	26 (52%)
EOSINOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
#HEPATIC SEROSA	(50)	(50)	(50)
FIBROSIS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		1 (2%)
CYTOPLASMIC VACUOLIZATION	2 (4%)		
#LIVER/PERIPORTAL	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	18 (36%)	25 (50%)	18 (36%)
#PANCREAS	(50)	(49)	(48)
DILATATION/DUCTS		1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
ATROPHY, NOS	9 (18%)	11 (22%)	7 (15%)
#ESOPHAGUS	(49)	(47)	(49)
INFLAMMATION, CHRONIC			2 (4%)
#STOMACH	(50)	(50)	(48)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#GASTRIC SEROSA	(50)	(50)	(48)
FIBROSIS			1 (2%)
#FORESTOMACH	(50)	(50)	(48)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS	4 (8%)	2 (4%)	14 (29%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAMINATION			2 (4%)
MINERALIZATION	8 (16%)	8 (16%)	6 (12%)
HYDRONEPHROSIS	2 (4%)		
CYST, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
NEPHROPATHY	9 (18%)	9 (18%)	3 (6%)
METAMORPHOSIS FATTY			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS	39 (78%)	25 (50%)	34 (68%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
#URINARY BLADDER	(48)	(50)	(48)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (6%)
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(50)
CYST, NOS	19 (39%)	24 (49%)	17 (34%)
HEMORRHAGE		1 (2%)	1 (2%)
HEMOSIDEROSIS	1 (2%)		
HYPERTROPHY, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	7 (14%)	8 (16%)	7 (14%)
ANGIECTASIS	5 (10%)	3 (6%)	3 (6%)
#PITUITARY INTERMEDIA	(49)	(49)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)		1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
LIPOIDOSIS	9 (18%)	7 (14%)	4 (8%)
HYPERTROPHY, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	4 (8%)	2 (4%)	3 (6%)
#ADRENAL MEDULLA	(50)	(50)	(50)
FOCAL CELLULAR CHANGE	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)		1 (2%)
#THYROID	(49)	(49)	(47)
CYST, NOS	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HYPERPLASIA, C-CELL	26 (53%)	21 (43%)	22 (47%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#PARATHYROID	(32)	(39)	(34)
ATROPHY, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)	1 (2%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION CHRONIC SUPPURATIVE		1 (2%)	
INFLAMMATION, GRANULOMATOUS	2 (4%)	4 (8%)	3 (6%)
#UTERUS	(45)	(48)	(49)
PROLAPSE		1 (2%)	
HYDROMETRA	1 (2%)		
CYST, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION CHRONIC SUPPURATIVE			1 (2%)
#CERVIX UTERI	(45)	(48)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
#UTERUS/ENDOMETRIUM	(45)	(48)	(49)
CYST, NOS			1 (2%)
HYPERPLASIA, CYSTIC	3 (7%)	7 (15%)	1 (2%)
#OVARY	(45)	(48)	(49)
CYST, NOS	5 (11%)	2 (4%)	3 (6%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS	1 (2%)		
CATARACT	17 (34%)	13 (26%)	22 (44%)
PHTHISIS BULBI	3 (6%)	4 (8%)	
EYE/CHOROID	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
EYE/IRIS	(50)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	30 (60%)	28 (56%)	21 (42%)
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
GRANULOMA, NOS		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE			1 (2%)
HEMOSIDEROSIS	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	3 (6%)	8 (16%)	4 (8%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE			1 (2%)
FIBROSIS	1 (2%)	2 (4%)	2 (4%)
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
DEGENERATION, NOS	2	1	1
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF			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 HYDROGEN PHOSPHITE

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

	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)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(47)	(50)
EDEMA, NOS	1 (2%)		
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(47)	(50)
FOREIGN BODY, NOS		1 (2%)	
CYST, NOS	1 (2%)		
#LUNG	(50)	(47)	(50)
CONGESTION, NOS		3 (6%)	2 (4%)
HEMORRHAGE	1 (2%)	2 (4%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	5 (11%)	2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
HISTIOCYTOSIS	1 (2%)		
#LUNG/ALVEOLI	(50)	(47)	(50)
HISTIOCYTOSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(50)
MYELOPROLIFERATIVE DISORDER		1 (2%)	
#BONE MARROW	(49)	(47)	(48)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, GRANULOCYTIC	1 (2%)		
#SPLEEN	(50)	(47)	(49)
HYPERPLASIA, LYMPHOID	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIESIS	5 (10%)	4 (9%)	4 (8%)
ERYTHROPOIESIS		1 (2%)	
#SPLENIC FOLLICLES	(50)	(47)	(49)
ATROPHY, NOS			1 (2%)
#LYMPH NODE	(27)	(26)	(25)
INFLAMMATION, ACUTE/CHRONIC		1 (4%)	
#MANDIBULAR L. NODE	(27)	(26)	(25)
PLASMACYTOSIS			1 (4%)
HYPERPLASIA, LYMPHOID			1 (4%)
#MESENTERIC L. NODE	(27)	(26)	(25)
CYST, NOS			1 (4%)
CONGESTION, NOS	3 (11%)	1 (4%)	
HEMORRHAGE		1 (4%)	
HYPERPLASIA, LYMPHOID		4 (15%)	1 (4%)
HEMATOPOIESIS	3 (11%)	4 (15%)	3 (12%)
#INGUINAL LYMPH NODE	(27)	(26)	(25)
NECROSIS, NOS			1 (4%)
HYPERPLASIA, RETICULUM CELL			1 (4%)
#LIVER	(50)	(47)	(50)
HEMATOPOIESIS		1 (2%)	1 (2%)
ERYTHROPOIESIS		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#DUODENUM	(46)	(39)	(43)
HYPERPLASIA, LYMPHOID		1 (3%)	
#JEJUNUM	(46)	(39)	(43)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(36)	(35)	(37)
INFLAMMATION, ACUTE		1 (3%)	
NECROSIS, NOS		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
#THYMIC LYMPHOCYTES	(36)	(35)	(37)
NECROSIS, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(27)	(26)	(25)
LYMPHANGIECTASIS			1 (4%)
#HEART	(50)	(47)	(50)
THROMBOSIS, NOS		1 (2%)	
CALCIFICATION, FOCAL		1 (2%)	
#MYOCARDIUM	(50)	(47)	(50)
MINERALIZATION		1 (2%)	
DEGENERATION, NOS	1 (2%)		
CALCIFICATION, FOCAL			1 (2%)
*PULMONARY ARTERY	(50)	(47)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(45)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#LIVER	(50)	(47)	(50)
HAMARTOMA	1 (2%)		
CYST, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	
HEMATOCELE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	2 (4%)	2 (4%)
FIBROSIS, FOCAL		1 (2%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL			2 (4%)
INFARCT, NOS	2 (4%)		2 (4%)
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	1 (2%)
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
BASOPHILIC CYTO CHANGE		2 (4%)	1 (2%)
GROUND-GLASS CYTO CHANGE	1 (2%)		
FOCAL CELLULAR CHANGE			1 (2%)
INCLUSION, CYTOPLASMIC			1 (2%)
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(47)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#LIVER/KUPFFER CELL	(50)	(47)	(50)
HYPERPLASIA, NOS	1 (2%)		
#LIVER/HEPATOCYTES	(50)	(47)	(50)
MULTINUCLEATE GIANT-CELL	1 (2%)		
#PANCREAS	(50)	(47)	(49)
CYST, NOS		1 (2%)	
CYSTIC DUCTS		1 (2%)	
#PANCREATIC ACINUS	(50)	(47)	(49)
ATROPHY, NOS	1 (2%)	1 (2%)	1 (2%)
ATROPHY, FOCAL	1 (2%)	3 (6%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#ESOPHAGUS	(46)	(46)	(48)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
#PERIESOPHAGEAL TISSUE	(46)	(46)	(48)
HEMORRHAGE	1 (2%)		
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
#STOMACH	(50)	(45)	(47)
MINERALIZATION		1 (2%)	
ULCER, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
EOSINOPHILIC INFILTRATE		2 (4%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ANGIECTASIS			1 (2%)
#GASTRIC MUCOSA	(50)	(45)	(47)
CYST, NOS	1 (2%)		
#GLANDULAR STOMACH	(50)	(45)	(47)
ABSCESS, NOS			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(45)	(47)
INFLAMMATION, ACUTE FOCAL			1 (2%)
#FORESTOMACH	(50)	(45)	(47)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(47)	(50)
MINERALIZATION		1 (2%)	
HYDRONEPHROSIS			1 (2%)
CYST, NOS	1 (2%)	1 (2%)	2 (4%)
PYELONEPHRITIS, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	19 (38%)	13 (28%)	13 (26%)
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NEPHROPATHY	2 (4%)		1 (2%)
CALCIFICATION, FOCAL	5 (10%)	4 (9%)	6 (12%)
ATROPHY, FOCAL		1 (2%)	
METAPLASIA, OSSEOUS		2 (4%)	
#KIDNEY/CORTEX	(50)	(47)	(50)
ATROPHY, FOCAL			2 (4%)
#KIDNEY/TUBULE	(50)	(47)	(50)
DEGENERATION, HYALINE	1 (2%)		
NECROSIS, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION			2 (4%)
#URINARY BLADDER	(50)	(46)	(46)
CALCULUS,GROSS OBSERVATION ONLY			1 (2%)
HEMORRHAGE	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)		1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(45)	(48)
CYST, NOS	2 (4%)	2 (4%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(50)	(46)	(49)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
FOCAL CELLULAR CHANGE		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL CORTEX	(50)	(46)	(49)
ACCESSORY STRUCTURE		1 (2%)	
HEMATOMA, NOS		1 (2%)	
DEGENERATION, NOS		1 (2%)	2 (4%)
FOCAL CELLULAR CHANGE	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)	2 (4%)	2 (4%)
#ADRENAL MEDULLA	(50)	(46)	(49)
FIBROSIS, FOCAL	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
#THYROID	(44)	(45)	(49)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	2 (5%)	2 (4%)	5 (10%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(47)	(50)
INFLAMMATION, ACUTE	1 (2%)		
*PREPUTIAL GLAND	(50)	(47)	(50)
DILATATION, NOS	2 (4%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
ABSCESS, NOS			2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#PROSTATE	(46)	(44)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	3 (7%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
*SEMINAL VESICLE	(50)	(47)	(50)
DILATATION, NOS	2 (4%)	1 (2%)	1 (2%)
*COAGULATING GLAND	(50)	(47)	(50)
DILATATION, NOS	2 (4%)		2 (4%)
#TESTIS	(50)	(47)	(50)
MINERALIZATION			2 (4%)
CALCIFICATION, NOS			1 (2%)
CALCIFICATION, FOCAL	2 (4%)	9 (19%)	24 (48%)
ATROPHY, NOS		1 (2%)	
#TESTIS/TUBULE	(50)	(47)	(50)
CALCIFICATION, FOCAL	1 (2%)		1 (2%)
CYTOMEGALY			1 (2%)
ATROPHY, FOCAL	1 (2%)		
#SPERMATID	(50)	(47)	(50)
CYTOMEGALY		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(47)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	1 (2%)
#LATERAL VENTRICLE	(50)	(47)	(49)
DILATATION, NOS	1 (2%)		
*CHOROID PLEXUS	(50)	(47)	(50)
HEMOSIDEROSIS		1 (2%)	
#BRAIN	(50)	(47)	(49)
CALCIFICATION, FOCAL	22 (44%)	15 (32%)	23 (47%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(47)	(50)
VEGETABLE FOREIGN BODY		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, FIBRINOUS		1 (2%)	
ABSCESS, NOS		1 (2%)	
FOREIGN MATERIAL, NOS		1 (2%)	
*ABDOMINAL CAVITY	(50)	(47)	(50)
NECROSIS, FAT	1 (2%)	1 (2%)	
*PERITONEUM	(50)	(47)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
*PLEURA	(50)	(47)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*EPICARDIUM	(50)	(47)	(50)
INFLAMMATION, FIBRINOUS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	2	
ANIMAL MISSING/NO NECROPSY		3	
AUTO/NECROPSY/HISTO PERF			1

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 HYDROGEN PHOSPHITE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
ULCER, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
MINERALIZATION	1 (2%)		
ATELECTASIS	2 (4%)		1 (2%)
CONGESTION, NOS	1 (2%)		1 (2%)
HEMORRHAGE	1 (2%)		2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	9 (18%)	7 (14%)	15 (30%)
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)
PNEUMONIA, ASPIRATION			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#LUNG/ALVEOLI	(50)	(49)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MYELOPROLIFERATIVE DISORDER		1 (2%)	
#BONE MARROW	(48)	(49)	(48)
MYELOFIBROSIS	37 (77%)	38 (78%)	37 (77%)
#SPLEEN	(50)	(48)	(48)
HYPERPLASIA, LYMPHOID	2 (4%)	2 (4%)	3 (6%)
HEMATOPOIESIS	2 (4%)	5 (10%)	2 (4%)
#MANDIBULAR L. NODE	(39)	(37)	(33)
HYPERPLASIA, LYMPHOID	1 (3%)	1 (3%)	1 (3%)
#MESENTERIC L. NODE	(39)	(37)	(33)
HEMORRHAGE		1 (3%)	
ABSCESS, NOS			1 (3%)
#LIVER	(50)	(49)	(50)
HEMATOPOIESIS		2 (4%)	1 (2%)
#JEJUNUM	(47)	(49)	(45)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(44)	(38)	(45)
ULTIMOBRANCHIAL CYST			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (5%)	
#THYMIC LYMPHOCYTES	(44)	(38)	(45)
NECROSIS, NOS			1 (2%)
CIRCULATORY SYSTEM			
#LYMPH NODE	(39)	(37)	(33)
LYMPHANGIECTASIS		1 (3%)	
#HEART	(50)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*PULMONARY ARTERY	(50)	(49)	(50)
MINERALIZATION	1 (2%)		
CALCIFICATION, FOCAL			1 (2%)
*MESENTERIC ARTERY	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*OVARIAN ARTERY	(50)	(49)	(50)
NECROSIS, FIBRINOID		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(47)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
#LIVER	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	4 (8%)
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		3 (6%)
METAMORPHOSIS FATTY		1 (2%)	4 (8%)
LIPOIDOSIS			1 (2%)
BASOPHILIC CYTO CHANGE	1 (2%)	3 (6%)	
#PORTAL TRACT	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#LIVER/HEPATOCYTES	(50)	(49)	(50)
HYPERTROPHY, NOS	1 (2%)		
#PANCREAS	(49)	(49)	(49)
CYST, NOS	1 (2%)		
CYSTIC DUCTS		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (2%)		
#PANCREATIC ACINUS	(49)	(49)	(49)
ATROPHY, NOS		1 (2%)	2 (4%)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(49)	(49)	(49)
ULCER, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#GASTRIC MUCOSA	(49)	(49)	(49)
NECROSIS, FOCAL			1 (2%)
#GASTRIC SUBMUCOSA	(49)	(49)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
#FORESTOMACH	(49)	(49)	(49)
ULCER, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#PEYER'S PATCH	(47)	(49)	(45)
HYPERPLASIA, NOS		1 (2%)	
#DUODENUM	(47)	(49)	(45)
ULCER, NOS			1 (2%)
#JEJUNUM	(47)	(49)	(45)
EOSINOPHILIC GRANULOMA	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
HYDRONEPHROSIS	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	18 (36%)	15 (31%)	16 (33%)
GLOMERULONEPHRITIS, MEMBRANOUS		1 (2%)	
GLOMERULONEPHRITIS, CHRONIC	1 (2%)		
NEPHROSIS, NOS	1 (2%)		
AMYLOIDOSIS		1 (2%)	1 (2%)
CALCIFICATION, FOCAL			1 (2%)
ATROPHY, FOCAL		2 (4%)	
METAPLASIA, OSSEOUS	1 (2%)		1 (2%)
#KIDNEY/INTERST.TISSUE	(50)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#KIDNEY/CORTEX	(50)	(49)	(49)
ATROPHY, FOCAL	3 (6%)	2 (4%)	2 (4%)
#KIDNEY/PELVIS	(50)	(49)	(49)
INFLAMMATION, CHRONIC		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#URINARY BLADDER	(48)	(44)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	14 (29%)	17 (39%)	16 (34%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#U. BLADDER/MUCOSA	(48)	(44)	(47)
INFLAMMATION, ACUTE		1 (2%)	
#U. BLADDER/SUBMUCOSA	(48)	(44)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(45)	(48)
CYST, NOS	2 (4%)	3 (7%)	1 (2%)
HEMORRHAGIC CYST			1 (2%)
HEMATOCELE	1 (2%)		
HYPERPLASIA, FOCAL	7 (15%)	8 (18%)	7 (15%)
ANGIECTASIS			3 (6%)
#ANTERIOR PITUITARY	(46)	(45)	(48)
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS			1 (2%)
#ADRENAL	(49)	(45)	(47)
CYST, NOS		1 (2%)	
CONGESTION, NOS			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		
#ADRENAL CORTEX	(49)	(45)	(47)
DEGENERATION, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(49)	(45)	(47)
HYPERPLASIA, FOCAL		1 (2%)	2 (4%)
#PERIADRENAL TISSUE	(49)	(45)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#THYROID	(47)	(48)	(48)
FOLLICULAR CYST, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	1 (2%)
ATROPHY, FOCAL			1 (2%)
HYPERPLASIA, DIFFUSE			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	5 (10%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
LACTATION	1 (2%)	1 (2%)	4 (8%)
*MAMMARY DUCT	(50)	(49)	(50)
FIBROSIS, FOCAL			1 (2%)
*MAMMARY LOBULE	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#UTERUS	(49)	(49)	(49)
HYDROMETRA		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, FIBRINOUS		1 (2%)	
#UTERUS/ENDOMETRIUM	(49)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	43 (88%)	41 (84%)	41 (84%)
#OVARY	(47)	(48)	(49)
CYST, NOS	10 (21%)	5 (10%)	7 (14%)
MULTIPLE CYSTS	1 (2%)		
HEMORRHAGIC CYST			1 (2%)
HEMATOCELE	1 (2%)		
ANGIECTASIS		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	2 (4%)	2 (4%)
#BRAIN	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
PERIVASCULAR CUFFING			1 (2%)
CALCIFICATION, FOCAL	20 (40%)	20 (41%)	23 (46%)
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(50)
INFLAMMATION CHRONIC SUPPURATIVE			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	3 (6%)	
ADIPOSE TISSUE			
INFLAMMATION, ACUTE NECROTIZING			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
ANIMAL MISSING/NO NECROPSY		1	

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 HYDROGEN PHOSPHITE

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

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.7%	3.3%	9.5%
Terminal Rates (c)	3/39 (8%)	1/30 (3%)	1/26 (4%)
Life Table Tests (d)	P=0.438	P=0.403N	P=0.497
Incidental Tumor Tests (d)	P=0.579	P=0.403N	P=0.661N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test		P=0.309N	P=0.661
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	7.7%	3.3%	13.2%
Terminal Rates (c)	3/39 (8%)	1/30 (3%)	2/26 (8%)
Life Table Tests (d)	P=0.259	P=0.403N	P=0.316
Incidental Tumor Tests (d)	P=0.373	P=0.403N	P=0.477
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test		P=0.309N	P=0.500
Lung: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	14.2%
Terminal Rates (c)	0/39 (0%)	0/30 (0%)	1/26 (4%)
Life Table Tests (d)	P=0.004	(e)	P=0.020
Incidental Tumor Tests (d)	P=0.034	(e)	P=0.141
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test		(e)	P=0.028
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	15.2%
Terminal Rates (c)	0/39 (0%)	0/30 (0%)	2/26 (8%)
Life Table Tests (d)	P=0.004	(e)	P=0.018
Incidental Tumor Tests (d)	P=0.017	(e)	P=0.074
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test		(e)	P=0.028
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	20/50 (40%)
Adjusted Rates (b)	0.0%	3.3%	63.5%
Terminal Rates (c)	0/39 (0%)	1/30 (3%)	15/26 (58%)
Life Table Tests (d)	P<0.001	P=0.448	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.448	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P=0.500	P<0.001
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	24/50 (48%)
Adjusted Rates (b)	0.0%	3.3%	71.8%
Terminal Rates (c)	0/39 (0%)	1/30 (3%)	17/26 (65%)
Life Table Tests (d)	P<0.001	P=0.448	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.448	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P=0.500	P<0.001
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	15/50 (30%)	13/50 (26%)
Adjusted Rates (b)	21.1%	39.0%	36.3%
Terminal Rates (c)	6/39 (15%)	7/30 (23%)	6/26 (23%)
Life Table Tests (d)	P=0.068	P=0.048	P=0.084
Incidental Tumor Tests (d)	P=0.458	P=0.196	P=0.467
Cochran-Armitage Trend Test (d)	P=0.208		
Fisher Exact Test		P=0.121	P=0.235

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

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.2%	0.0%	0.0%
Terminal Rates (c)	2/39 (5%)	0/30 (0%)	0/26 (0%)
Life Table Tests (d)	P=0.061N	P=0.169N	P=0.180N
Incidental Tumor Tests (d)	P=0.022N	P=0.109N	P=0.074N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test		P=0.121N	P=0.121N
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.3%	10.8%
Terminal Rates (c)	0/39 (0%)	1/30 (3%)	2/26 (8%)
Life Table Tests (d)	P=0.032	P=0.448	P=0.067
Incidental Tumor Tests (d)	P=0.052	P=0.448	P=0.115
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test		P=0.500	P=0.121
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	10.1%
Terminal Rates (c)	0/39 (0%)	0/30 (0%)	1/26 (4%)
Life Table Tests (d)	P=0.023	(e)	P=0.074
Incidental Tumor Tests (d)	P=0.066	(e)	P=0.196
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test		(e)	P=0.121
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	0.0%	3.3%	20.0%
Terminal Rates (c)	0/39 (0%)	1/30 (3%)	3/26 (12%)
Life Table Tests (d)	P=0.002	P=0.448	P=0.006
Incidental Tumor Tests (d)	P=0.006	P=0.448	P=0.025
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test		P=0.500	P=0.013
Pituitary: Adenoma			
Overall Rates (a)	16/48 (33%)	8/50 (16%)	14/48 (29%)
Adjusted Rates (b)	37.8%	24.2%	45.3%
Terminal Rates (c)	13/39 (33%)	6/30 (20%)	10/26 (38%)
Life Table Tests (d)	P=0.329	P=0.173N	P=0.316
Incidental Tumor Tests (d)	P=0.501N	P=0.069N	P=0.563
Cochran-Armitage Trend Test (d)	P=0.364N		
Fisher Exact Test		P=0.039N	P=0.413N
Adrenal: Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	9/50 (18%)	3/50 (6%)
Adjusted Rates (b)	15.4%	27.9%	11.5%
Terminal Rates (c)	6/39 (15%)	7/30 (23%)	3/26 (12%)
Life Table Tests (d)	P=0.483N	P=0.134	P=0.471N
Incidental Tumor Tests (d)	P=0.387N	P=0.173	P=0.471N
Cochran-Armitage Trend Test (d)	P=0.221N		
Fisher Exact Test		P=0.288	P=0.243N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	4/47 (9%)	3/49 (6%)
Adjusted Rates (b)	5.1%	12.8%	9.5%
Terminal Rates (c)	2/39 (5%)	3/29 (10%)	1/26 (4%)
Life Table Tests (d)	P=0.263	P=0.221	P=0.353
Incidental Tumor Tests (d)	P=0.454	P=0.275	P=0.532
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test		P=0.310	P=0.490

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

	Vehicle Control	100 mg/kg	200 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	4/47 (9%)	3/49 (6%)
Adjusted Rates (b)	9.8%	12.8%	9.5%
Terminal Rates (c)	3/39 (8%)	3/29 (10%)	1/26 (4%)
Life Table Tests (d)	P=0.539	P=0.492	P=0.635
Incidental Tumor Tests (d)	P=0.368N	P=0.582	P=0.442N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test		P=0.607	P=0.511N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	42/50 (84%)	37/49 (76%)	35/50 (70%)
Adjusted Rates (b)	91.3%	97.3%	91.8%
Terminal Rates (c)	35/39 (90%)	29/30 (97%)	23/26 (88%)
Life Table Tests (d)	P=0.106	P=0.197	P=0.148
Incidental Tumor Tests (d)	P=0.108N	P=0.557N	P=0.127N
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test		P=0.212N	P=0.077N
Testis: Mesothelioma			
Overall Rates (a)	4/50 (8%)	1/49 (2%)	1/50 (2%)
Adjusted Rates (b)	8.6%	2.2%	3.8%
Terminal Rates (c)	0/39 (0%)	0/30 (0%)	1/26 (4%)
Life Table Tests (d)	P=0.139N	P=0.227N	P=0.241N
Incidental Tumor Tests (d)	P=0.024N	P=0.056N	P=0.034N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test		P=0.188N	P=0.181N
All Sites: Mesothelioma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	13.3%	7.7%	5.8%
Terminal Rates (c)	2/39 (5%)	1/30 (3%)	1/26 (4%)
Life Table Tests (d)	P=0.152N	P=0.341N	P=0.218N
Incidental Tumor Tests (d)	P=0.046N	P=0.111N	P=0.044N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test		P=0.244N	P=0.135N

(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 rates. 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 100 mg/kg and vehicle control groups.

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

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.9%	8.8%
Terminal Rates (c)	0/40 (0%)	1/35 (3%)	3/34 (9%)
Life Table Tests (d)	P=0.047	P=0.473	P=0.094
Incidental Tumor Tests (d)	P=0.047	P=0.473	P=0.094
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Test		P=0.495	P=0.121
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	7/50 (14%)	7/50 (14%)
Adjusted Rates (b)	12.8%	18.0%	17.4%
Terminal Rates (c)	2/40 (5%)	5/35 (14%)	3/34 (9%)
Life Table Tests (d)	P=0.368	P=0.438	P=0.434
Incidental Tumor Tests (d)	P=0.490	P=0.534	P=0.529
Cochran-Armitage Trend Test (d)	P=0.442		
Fisher Exact Test		P=0.500	P=0.500
Pituitary: Adenoma			
Overall Rates (a)	18/49 (37%)	17/49 (35%)	24/50 (48%)
Adjusted Rates (b)	39.7%	42.5%	56.3%
Terminal Rates (c)	13/40 (33%)	12/34 (35%)	16/34 (47%)
Life Table Tests (d)	P=0.067	P=0.487	P=0.081
Incidental Tumor Tests (d)	P=0.156	P=0.515N	P=0.220
Cochran-Armitage Trend Test (d)	P=0.148		
Fisher Exact Test		P=0.500N	P=0.176
Adrenal: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	9.4%	8.6%	13.3%
Terminal Rates (c)	2/40 (5%)	3/35 (9%)	3/34 (9%)
Life Table Tests (d)	P=0.358	P=0.548N	P=0.431
Incidental Tumor Tests (d)	P=0.408	P=0.508N	P=0.542
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test		P=0.500N	P=0.500
Thyroid: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	1/49 (2%)	4/47 (9%)
Adjusted Rates (b)	7.5%	2.9%	11.8%
Terminal Rates (c)	3/40 (7%)	1/34 (3%)	4/34 (12%)
Life Table Tests (d)	P=0.338	P=0.365N	P=0.411
Incidental Tumor Tests (d)	P=0.338	P=0.365N	P=0.411
Cochran-Armitage Trend Test (d)	P=0.392		
Fisher Exact Test		P=0.309N	P=0.476
Mammary Gland: Fibroadenoma			
Overall Rates (a)	9/50 (18%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (b)	21.2%	30.8%	37.1%
Terminal Rates (c)	7/40 (18%)	9/35 (26%)	11/34 (32%)
Life Table Tests (d)	P=0.081	P=0.229	P=0.097
Incidental Tumor Tests (d)	P=0.091	P=0.245	P=0.124
Cochran-Armitage Trend Test (d)	P=0.144		
Fisher Exact Test		P=0.312	P=0.171
Clitoral Gland: Adenoma, Cystadenoma, or Squamous Cell Papilloma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	4.5%	7.8%	5.9%
Terminal Rates (c)	1/40 (3%)	1/35 (3%)	2/34 (6%)
Life Table Tests (d)	P=0.535	P=0.461	P=0.643
Incidental Tumor Tests (d)	P=0.568N	P=0.636	P=0.635
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test		P=0.500	P=0.691

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL HYDROGEN PHOSPHITE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/45 (22%)	10/48 (21%)	9/49 (18%)
Adjusted Rates (b)	27.8%	27.9%	26.2%
Terminal Rates (c)	10/36 (28%)	8/33 (24%)	8/33 (24%)
Life Table Tests (d)	P=0.535N	P=0.520	P=0.585N
Incidental Tumor Tests (d)	P=0.460N	P=0.570N	P=0.537N
Cochran-Armitage Trend Test (d)	P=0.368N		
Fisher Exact Test		P=0.535N	P=0.417N

(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 rates. 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 HYDROGEN PHOSPHITE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	2/47 (4%)	3/50 (6%)
Adjusted Rates (b)	14.3%	5.9%	8.5%
Terminal Rates (c)	6/42 (14%)	2/34 (6%)	2/32 (6%)
Life Table Tests (d)	P=0.276N	P=0.210N	P=0.375N
Incidental Tumor Tests (d)	P=0.257N	P=0.210N	P=0.347N
Cochran-Armitage Trend Test (d)	P=0.171N		
Fisher Exact Test		P=0.156N	P=0.244N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	6/50 (12%)	5/47 (11%)	8/50 (16%)
Adjusted Rates (b)	13.8%	14.7%	22.5%
Terminal Rates (c)	5/42 (12%)	5/34 (15%)	5/32 (16%)
Life Table Tests (d)	P=0.183	P=0.609	P=0.230
Incidental Tumor Tests (d)	P=0.391	P=0.602	P=0.511
Cochran-Armitage Trend Test (d)	P=0.327		
Fisher Exact Test		P=0.544N	P=0.387
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	7/47 (15%)	11/50 (22%)
Adjusted Rates (b)	27.8%	20.6%	30.0%
Terminal Rates (c)	11/42 (26%)	7/34 (21%)	7/32 (22%)
Life Table Tests (d)	P=0.402	P=0.299N	P=0.434
Incidental Tumor Tests (d)	P=0.469N	P=0.305N	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.451N		
Fisher Exact Test		P=0.192N	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	1/47 (2%)	2/50 (4%)
Adjusted Rates (b)	7.1%	2.9%	6.2%
Terminal Rates (c)	3/42 (7%)	1/34 (3%)	2/32 (6%)
Life Table Tests (d)	P=0.511N	P=0.383N	P=0.623N
Incidental Tumor Tests (d)	P=0.511N	P=0.383N	P=0.623N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test		P=0.333N	P=0.500N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	5/50 (10%)	1/47 (2%)	2/50 (4%)
Adjusted Rates (b)	11.6%	2.9%	6.2%
Terminal Rates (c)	4/42 (10%)	1/34 (3%)	2/32 (6%)
Life Table Tests (d)	P=0.213N	P=0.160N	P=0.329N
Incidental Tumor Tests (d)	P=0.130N	P=0.117N	P=0.209N
Cochran-Armitage Trend Test (d)	P=0.135N		
Fisher Exact Test		P=0.117N	P=0.218N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	(e) 2/47 (4%)	4/50 (8%)
Adjusted Rates (b)	2.4%	5.7%	10.7%
Terminal Rates (c)	1/42 (2%)	1/34 (3%)	0/32 (0%)
Life Table Tests (d)	P=0.087	P=0.430	P=0.135
Incidental Tumor Tests (d)	P=0.497	P=0.529	P=0.594
Cochran-Armitage Trend Test (d)	P=0.120		
Fisher Exact Test		P=0.447	P=0.181
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	(e) 3/47 (6%)	4/50 (8%)
Adjusted Rates (b)	2.4%	8.6%	10.7%
Terminal Rates (c)	1/42 (2%)	2/34 (6%)	0/32 (0%)
Life Table Tests (d)	P=0.094	P=0.238	P=0.135
Incidental Tumor Tests (d)	P=0.478	P=0.307	P=0.594
Cochran-Armitage Trend Test (d)	P=0.135		
Fisher Exact Test		P=0.285	P=0.181

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

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	12/50 (24%)	8/47 (17%)	8/50 (16%)
Adjusted Rates (b)	27.0%	23.5%	25.0%
Terminal Rates (c)	10/42 (24%)	8/34 (24%)	8/32 (25%)
Life Table Tests (d)	P=0.391N	P=0.404N	P=0.447N
Incidental Tumor Tests (d)	P=0.372N	P=0.417N	P=0.420N
Cochran-Armitage Trend Test (d)	P=0.186N		
Fisher Exact Test		P=0.276N	P=0.227N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	2/47 (4%)	7/50 (14%)
Adjusted Rates (b)	20.8%	5.6%	18.8%
Terminal Rates (c)	8/42 (19%)	1/34 (3%)	4/32 (13%)
Life Table Tests (d)	P=0.474N	P=0.060N	P=0.576N
Incidental Tumor Tests (d)	P=0.322N	P=0.038N	P=0.413N
Cochran-Armitage Trend Test (d)	P=0.324N		
Fisher Exact Test		P=0.033N	P=0.393N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	10/47 (21%)	13/50 (26%)
Adjusted Rates (b)	42.0%	28.5%	36.2%
Terminal Rates (c)	16/42 (38%)	9/34 (26%)	10/32 (31%)
Life Table Tests (d)	P=0.319N	P=0.133N	P=0.389N
Incidental Tumor Tests (d)	P=0.209N	P=0.109N	P=0.247N
Cochran-Armitage Trend Test (d)	P=0.112N		
Fisher Exact Test		P=0.057N	P=0.142N
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	0/46 (0%)	0/49 (0%)
Adjusted Rates (b)	7.1%	0.0%	0.0%
Terminal Rates (c)	3/42 (7%)	0/34 (0%)	0/31 (0%)
Life Table Tests (d)	P=0.060N	P=0.161N	P=0.180N
Incidental Tumor Tests (d)	P=0.060N	P=0.161N	P=0.180N
Cochran-Armitage Trend Test (d)	P=0.040N		
Fisher Exact Test		P=0.137N	P=0.125N
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	3/44 (7%)	0/45 (0%)	1/49 (2%)
Adjusted Rates (b)	8.3%	0.0%	3.1%
Terminal Rates (c)	3/36 (8%)	0/33 (0%)	1/32 (3%)
Life Table Tests (d)	P=0.203N	P=0.136N	P=0.348N
Incidental Tumor Tests (d)	P=0.203N	P=0.136N	P=0.348N
Cochran-Armitage Trend Test (d)	P=0.154N		
Fisher Exact Test		P=0.117N	P=0.269N

(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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Diagnosed as angiosarcoma

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	5.0%	7.3%	2.9%
Terminal Rates (c)	1/39 (3%)	2/38 (5%)	1/35 (3%)
Life Table Tests (d)	P=0.435N	P=0.483	P=0.537N
Incidental Tumor Tests (d)	P=0.371N	P=0.650	P=0.507N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test		P=0.490	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	10.0%	7.3%	2.9%
Terminal Rates (c)	3/39 (8%)	2/38 (5%)	1/35 (3%)
Life Table Tests (d)	P=0.160N	P=0.519N	P=0.215N
Incidental Tumor Tests (d)	P=0.120N	P=0.379N	P=0.198N
Cochran-Armitage Trend Test (d)	P=0.134N		
Fisher Exact Test		P=0.511N	P=0.181N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	7/50 (14%)	5/49 (10%)	8/50 (16%)
Adjusted Rates (b)	17.4%	13.2%	21.4%
Terminal Rates (c)	6/39 (15%)	5/38 (13%)	6/35 (17%)
Life Table Tests (d)	P=0.362	P=0.400N	P=0.414
Incidental Tumor Tests (d)	P=0.392	P=0.420N	P=0.453
Cochran-Armitage Trend Test (d)	P=0.442		
Fisher Exact Test		P=0.394N	P=0.500
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	5/50 (10%)	4/49 (8%)	5/50 (10%)
Adjusted Rates (b)	11.8%	10.5%	14.3%
Terminal Rates (c)	3/39 (8%)	4/38 (11%)	5/35 (14%)
Life Table Tests (d)	P=0.503	P=0.522N	P=0.565
Incidental Tumor Tests (d)	P=0.526	P=0.568N	P=0.595
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Test		P=0.513N	P=0.630
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	6.7%	2.6%	0.0%
Terminal Rates (c)	1/39 (3%)	1/38 (3%)	0/35 (0%)
Life Table Tests (d)	P=0.072N	P=0.328N	P=0.139N
Incidental Tumor Tests (d)	P=0.083N	P=0.401N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test		P=0.316N	P=0.121N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	11/49 (22%)	16/50 (32%)
Adjusted Rates (b)	35.2%	28.9%	40.7%
Terminal Rates (c)	10/39 (26%)	11/38 (29%)	12/35 (34%)
Life Table Tests (d)	P=0.421	P=0.224N	P=0.455
Incidental Tumor Tests (d)	P=0.467	P=0.292N	P=0.518
Cochran-Armitage Trend Test (d)	P=0.544		
Fisher Exact Test		P=0.200N	P=0.585N
Hematopoietic System: Undifferentiated Leukemia			
Overall Rates (a)	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	4.1%	0.0%	6.7%
Terminal Rates (c)	0/39 (0%)	0/38 (0%)	0/35 (0%)
Life Table Tests (d)	P=0.365	P=0.267N	P=0.464
Incidental Tumor Tests (d)	P=0.383	P=0.347N	P=0.661
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test		P=0.253N	P=0.500

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	18/50 (36%)	11/49 (22%)	19/50 (38%)
Adjusted Rates (b)	37.9%	28.9%	44.6%
Terminal Rates (c)	10/39 (26%)	11/38 (29%)	12/35 (34%)
Life Table Tests (d)	P=0.341	P=0.133N	P=0.374
Incidental Tumor Tests (d)	P=0.384	P=0.191N	P=0.495
Cochran-Armitage Trend Test (d)	P=0.457		
Fisher Exact Test		P=0.103N	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	0/50 (0%)	6/49 (12%)	3/50 (6%)
Adjusted Rates (b)	0.0%	15.8%	8.6%
Terminal Rates (c)	0/39 (0%)	6/38 (16%)	3/35 (9%)
Life Table Tests (d)	P=0.115	P=0.016	P=0.102
Incidental Tumor Tests (d)	P=0.115	P=0.016	P=0.102
Cochran-Armitage Trend Test (d)	P=0.147		
Fisher Exact Test		P=0.012	P=0.121
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	6/49 (12%)	3/50 (6%)
Adjusted Rates (b)	5.1%	15.8%	8.6%
Terminal Rates (c)	2/39 (5%)	6/38 (16%)	3/35 (9%)
Life Table Tests (d)	P=0.364	P=0.125	P=0.450
Incidental Tumor Tests (d)	P=0.364	P=0.125	P=0.450
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test		P=0.128	P=0.500
Pituitary: Adenoma			
Overall Rates (a)	13/46 (28%)	9/45 (20%)	11/48 (23%)
Adjusted Rates (b)	31.2%	24.2%	28.4%
Terminal Rates (c)	10/38 (26%)	8/36 (22%)	8/35 (23%)
Life Table Tests (d)	P=0.447N	P=0.289N	P=0.501N
Incidental Tumor Tests (d)	P=0.358N	P=0.282N	P=0.401N
Cochran-Armitage Trend Test (d)	P=0.316N		
Fisher Exact Test		P=0.250N	P=0.360N

(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 rates. A negative trend 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 RECEIVING CORN OIL BY GAVAGE

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

Study	Incidence in Vehicle Controls Alveolar/Bronchiolar Adenoma	Alveolar/Bronchiolar Carcinoma	Alveolar/Bronchiolar Adenoma or Carcinoma	Squamous Cell Carcinoma
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	1/50	1/50	2/50	0/50
Tris(2-ethylhexyl)phosphate	0/50	1/50	1/50	0/50
Toluenediisocyanate	1/50	1/50	2/50	0/50
TOTAL	2/150 (1.3%)	3/150 (2.0%)	5/150 (3.3%)	0/150 (0.0%)
SD (b)	1.15%	0.00%	1.15%	0.00%
Range (c)				
High	1/50	1/50	2/50	0/50
Low	0/50	1/50	1/50	0/50
Overall Historical Incidence				
TOTAL	34/1,143 (3.0%)	16/1,143 (1.4%)	50/1,143 (4.4%)	2/1,143 (0.2%)
SD (b)	1.93%	1.53%	2.40%	0.58%
Range (c)				
High	3/48	3/50	4/50	1/50
Low	0/50	0/50	0/50	0/52

(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 LEUKEMIA IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	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 F3. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	1/50	1/50	2/50
Tris(2-ethylhexyl)phosphate	0/50	0/50	0/50
Toluenediisocyanate	7/50	0/50	7/50
TOTAL	8/150 (5.3%)	1/150 (0.7%)	9/150 (6.0%)
SD (b)	7.57%	1.15%	7.21%
Range (c)			
High	7/50	1/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	31/1,141 (2.7%)	9/1,141 (0.8%)	40/1,141 (3.5%)
SD (b)	3.36%	1.45%	3.66%
Range (c)			
High	7/50	2/50	7/50
Low	0/50	0/52	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 STOMACH TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	No. of Animals Examined	Number with Tumors	Site	Diagnosis
Incidence at Litton Bionetics, Inc.				
	147	No tumors reported		
Overall Historical Incidence				
	1,114	2	Stomach, NOS	Squamous cell papilloma
		1	Stomach, NOS	Squamous cell carcinoma
		2	Forestomach	Squamous cell papilloma
		1	Cardiac stomach	Squamous cell papilloma
TOTAL		5 papilloma 1 carcinoma		

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F5. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	0/50	0/50	0/50
Tris(2-ethylhexyl)phosphate	0/50	0/50	0/50
Toluenediisocyanate	0/50	1/50	1/50
TOTAL	0/150 (0.0%)	1/150 (0.7%)	1/150 (0.7%)
SD (b)	0.00%	1.15%	1.15%
Range (c)			
High	0/50	1/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	14/1,142 (1.2%)	10/1,142 (0.9%)	24/1,142 (2.1%)
SD (b)	1.91%	1.34%	2.07%
Range (c)			
High	4/49	2/48	4/49
Low	0/52	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 F6. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING 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.

TABLE F7. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Toluenediisocyanate	2/50	2/50	4/50
Diallylphthalate	0/50	1/50	1/50
Tris(2-ethylhexyl)phosphate	2/48	0/48	2/48
TOTAL	4/148 (2.7%)	3/148 (2.0%)	7/148 (4.7%)
SD (b)	2.36%	2.00%	3.04%
Range (c)			
High	2/48	2/50	4/50
Low	0/50	0/48	1/50
Overall Historical Incidence			
TOTAL	47/1,176 (4.0%)	34/1,176 (2.9%)	80/1,176 (6.8%)
SD (b)	2.55%	2.18%	3.37%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	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.

APPENDIX G

CHEMICAL CHARACTERIZATION OF DIMETHYL HYDROGEN PHOSPHITE

APPENDIX G. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. DM113077 Performed by Midwest Research Institute

A. Physical Properties

	Determined	Literature Values
1. Boiling Point:	175.2° ± 2(δ)° C at 739 mm (visual, micro boiling point)	72°-73° C at 25 mm (Condensed Chemical Dictionary, 1981)
2. Index of Refraction:	n_D^{20}: 1.4018 ± 0.0002(δ)	No literature reference found
3. Density:	d_{22}^{25}: 1.1954 ± 0.0004	d_4^{20}: 1.20 (Condensed Chemical Dictionary, 1981)
4. Appearance:	Clear, colorless liquid	

B. Spectral Data

1. Infrared	Determined	Literature Values
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	95% Ethanol	
Results:	No absorbance between 350 and 800 nm. No maximum between 216 and 350 nm, but a small absorbance (less than 0.05 absorbance units) was observed toward the short wavelength end.	No literature reference found. Spectrum consistent with structure.

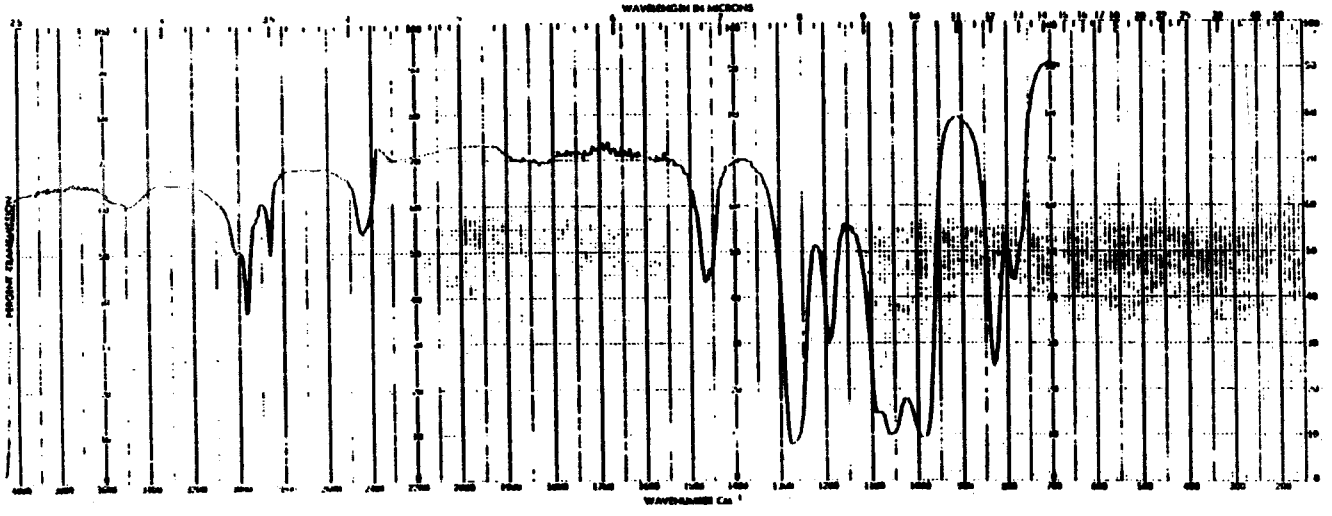

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. DM113077)

3. Nuclear Magnetic Resonance

	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with internal tetramethylsilane	
Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical Shift (δ):	a d, 3.75 ppm $J_{P\text{-}a}$ = 12 Hz b d, 6.75 ppm $J_{P\text{-}b}$ = 693 Hz c s, 3.35 ppm (impurity)	
Integration Ratios:	a 6.08 b 0.92 c No integration (impurity)	

C. Elemental Analyses:

Element	C	H	P
Theory (T)	21.83	6.41	28.14
Determined (D)	21.75 21.89	6.42 6.47	28.37
D/T (percent)	99.95	100.55	100.82

D. Chromatographic Analyses

1. Thin-Layer Chromatography

Plates: Silica Gel 60 F-254
Reference Standard: Tri-*n*-butyl phosphate (100 µg), 10 µg/µl in acetone.
Amount Spotted: 100 µg and 300 µg (10 µg/µl in acetone)
Visualization: Iodine vapor

System 1: Methanol:water (90:10)
R_f: 0.71 (major); 0.01 (slight trace); origin (very slight trace)
R_{st}: 0.86; 0.01; origin

System 2: 1,4-Dioxane (100%)
R_f: 0.42 (major); origin (trace)
R_{st}: 0.64; origin

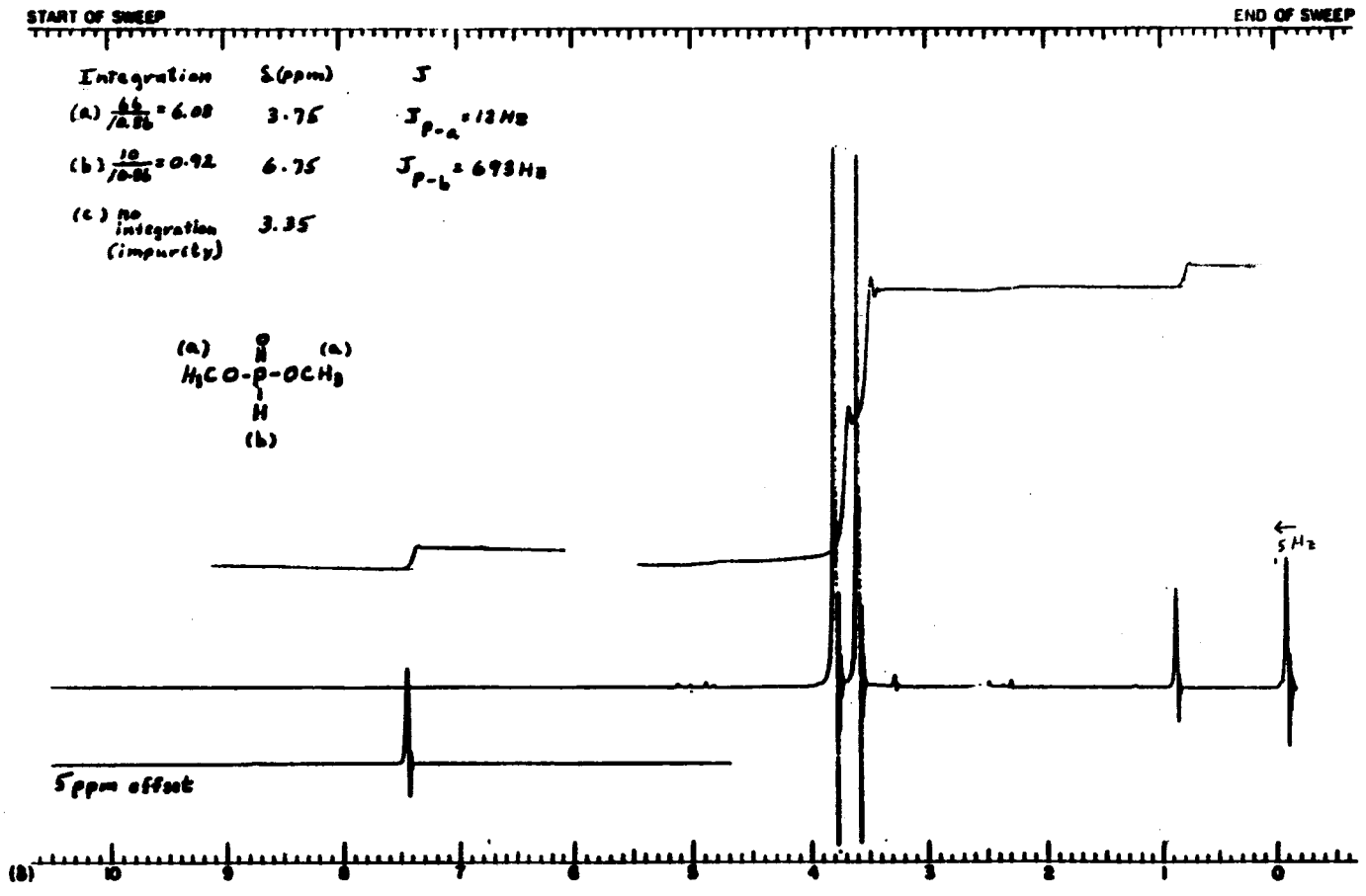

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. DM113077)

2. Gas Chromatography

Instrument: Tracor MT220
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 310° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

a. System 1:

Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°-170° at 10° C/min
Sample injected: Neat liquid (5 µl) and 1.0% and 0.5% dimethyl hydrogen phosphite in methylene chloride to quantitate the major peak and check for overloading.

Results: Major peak and 10 impurities. Two impurities had areas 1.4% and 1.5% relative to the major peak; the other eight impurities had a total area of 1.0% of the major peak area.

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.47	0.05	0.01
2	0.59	0.07	1.40
3	9.01	1.00	100
4	10.34	1.15	0.60
5	10.92	1.21	0.03
6	11.08	1.23	1.50
7	13.30	1.48	0.05
8	13.81	1.53	0.01
9	14.59	1.62	0.24
10	15.29	1.70	0.04
11	17.43	1.94	0.03

b. System 2:

Column: 10% Carbowax 20M-TPA on 80/100 Chromasorb W (AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°- 200° at 10° C/min
Sample injected: Neat liquid (5 µl) and 1.0% and 0.5% dimethyl hydrogen phosphite in methylene chloride to quantitate the major peak and check for overloading.

Results: Major peak and eight impurities. Two impurities had areas 1.6% and 1.0% of the major peak area; the other six impurities had a combined area of 1.3% relative to the major peak area.

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.33	0.03	0.02
2	1.72	0.14	1.60
3	4.64	0.37	0.05
4	12.40	1.00	100
5	12.93	1.04	0.39
6	13.03	1.05	0.22
7	13.24	1.07	0.35
8	14.04	1.13	1.00
9	15.52	1.25	0.24

E. Conclusions: Results of elemental analyses for carbon, hydrogen and phosphorus were in agreement with the theoretical values. Thin-layer chromatography by one system indicated one slight trace impurity and one very slight trace impurity. A second thin-layer chromatography system indicated one trace impurity. Gas chromatography by one system indicated 10 impurities. Two impurities had areas of 1.4% and 1.5% of the major peak area. The other eight impurities had a combined area of 1.0% of the major peak area. Another gas chromatography system indicated eight impurities. Two impurities had areas of 1.6% and 1.0% of the major peak area. The other six impurities totaled 1.3% of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure and literature spectra.

II. Identity and Purity Determinations of Lot No. KC031247 Performed by Midwest Research Institute

A. Physical Properties

1. Boiling Point:	Determined	Literature Values
	167.5° C at 745 mm (visual, micro boiling point)	72°-73° C at 25 mm (Condensed Chemical Dictionary, 1981)
2. Appearance:	Clear, colorless, nonviscous liquid	

B. Spectral Data

1. Infrared	Determined	Literature Values
Instrument:	Perkin-Elmer 283	
Cell:	Neat liquid between silver chloride plates, 0.2 mm thick	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	Absolute ethanol	
Results:	No absorbance between 350 and 800 nm using a 1% solution. In the ultraviolet region, a small increase in absorbance was noted in a 1% solution between 350-215 nm.	No literature reference found. Spectrum consistent with structure.

3. Nuclear Magnetic Resonance

	Determined	Literature Values
Instrument:	Varian EM-360	
Solvent:	Deuterated chloroform with tetramethylsilane as reference	
Assignments:	See Figure 8	Spectrum consistent with literature spectrum (Sadtler Standard Spectra)

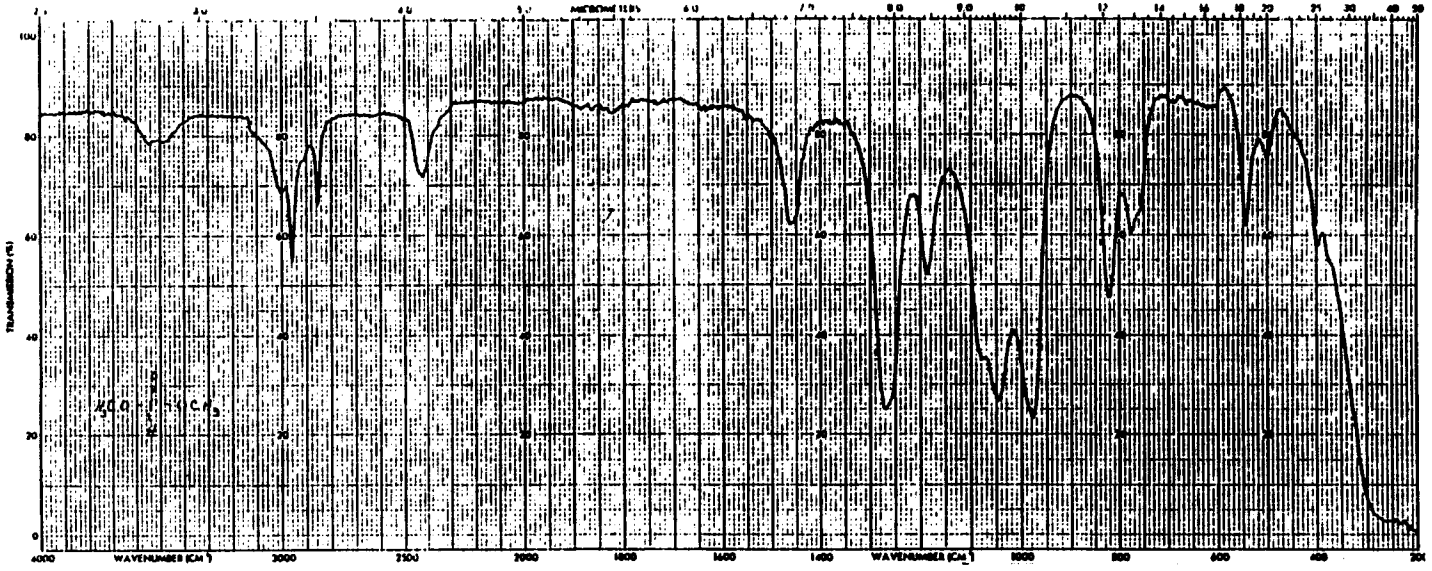

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. KC031247)

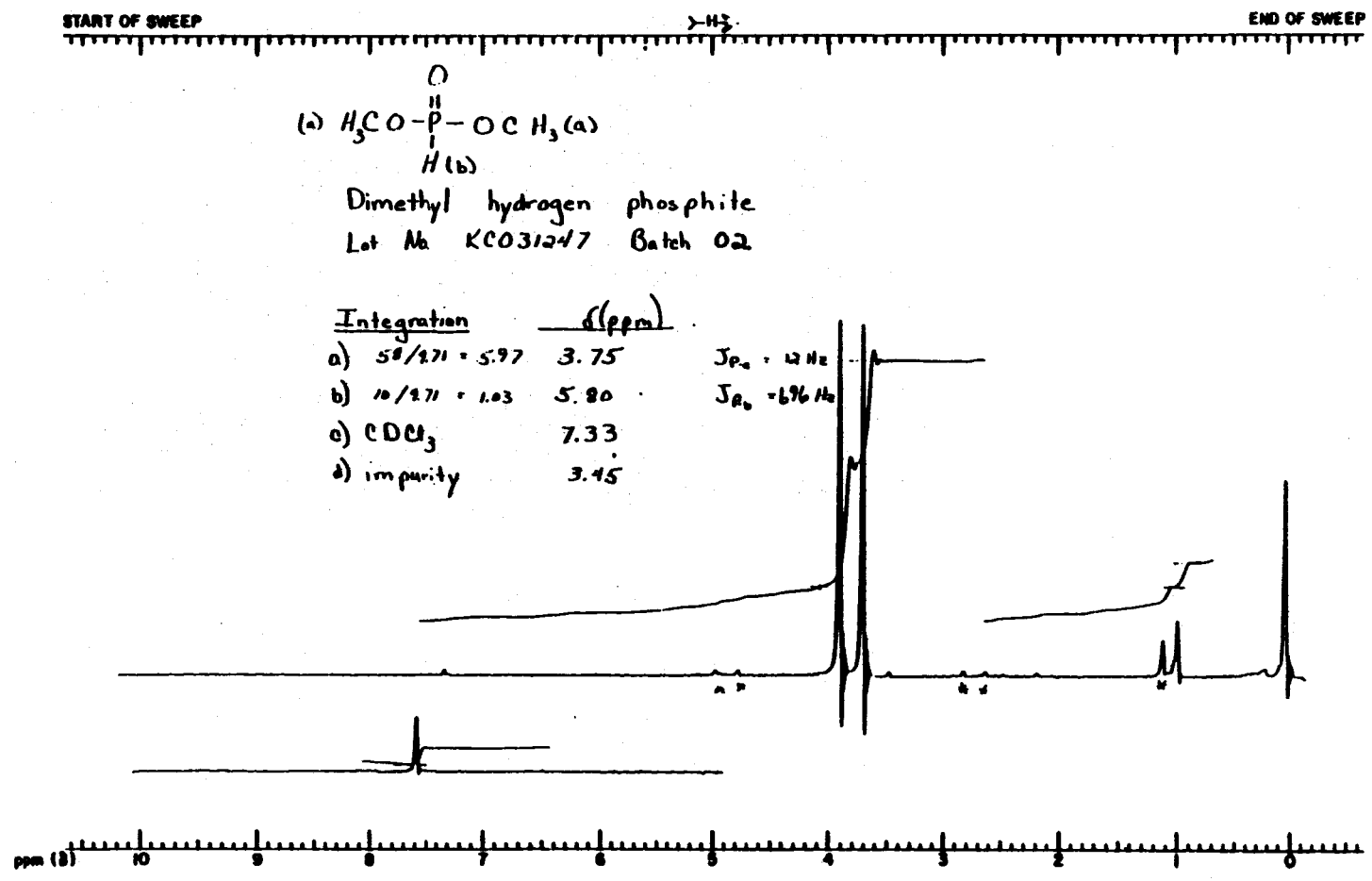

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. KC031247)

Chemical Shift (δ):	a d,	3.75 ppm	$J_{P\text{-}a}$ = 12 Hz
	b d,	5.80 ppm	$J_{P\text{-}b}$ = 696 Hz
	c	3.45 ppm	(impurity)
Integration Ratios:	a 5.98		
	b 1.03		
	c No integration (impurity)		

C. Elemental Analyses:

Element	C	H	P
Theory (T)	21.83	6.41	28.14
Determined (D)	22.11	6.63	27.73
	22.14	6.60	27.64
D/T (percent)	101.35	103.19	98.38

D. Titration:

1. Procedure: Six samples of dimethyl hydrogen phosphite were dissolved in absolute ethanol and reacted with excess 0.1N aqueous sodium hydroxide. The unreacted excess was then titrated potentiometrically with 0.1N aqueous hydrochloric acid (Bernhardt and Rattenbury, 1956).

2. Results: 97.5% ± 0.3(δ)%

E. Chromatographic Analyses

1. Thin-Layer Chromatography

Plates: Silica Gel 60 F-254, 0.25 mm thick
Reference Standard: 120 µg (12 µg/µl in acetone) of tributyl phosphate
Amount Spotted: 10, 50, 100 and 300 µg (10 µg/µl in acetone)
Visualization: Iodine vapor
Results:

Spot intensity	R_f	R_{st}
System 1: Methanol:water (90:10)		
Major	0.84	1.10
System 2: 1,4-Dioxane (100%)		
Major	0.74	0.82

2. Gas Chromatography

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 300° C
Carrier gas: Nitrogen

a. System 1:

Column: 10% Carbowax 20M-TPA on 80/100 Chromasorb W (AW), 1.8 m × 4 mm ID, silylated glass
Carrier flow rate: 70 ml/min
Oven temperature program: 5 min at 50° C, then 50°-200° C at 10° C/min
Sample injected: Neat liquid (2 µl) and 1.0% and 0.5% dimethyl hydrogen phosphite in methylene chloride to quantitate the major peak and check for overloading.

Results: A major peak and seven impurities, one preceding and six following the major, with relative areas greater than 0.1%. Their respective relative areas were 0.2%, 0.3%, 0.2%, 0.2%, 0.1%, 1.1%, and 0.2%. Two additional impurities, following the major peak and having relative areas less than 0.1%, were detected.

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.7	0.20	0.2
2	13.7	1.00	100
3 (shoulder)	14.2	1.04	0.3
4	14.4	1.05	0.2
5	14.8	1.08	0.2
6 (shoulder)	15.7	1.15	0.1
7	15.9	1.16	1.1
8	18.2	1.33	0.2

b. System 2:

Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, silylated glass
Carrier flow rate: 70 ml/min
Oven temperature program: 5 min at 50° C, then 50°-170° C at 10° C/min
Sample injected: Neat liquid (2 µl) and 1.0% and 0.5% dimethyl hydrogen phosphite in methylene chloride to quantitate the major peak and check for overloading.

Results: Four impurities, one preceding and three following the major peak, were detected with relative areas greater than 0.1%. Three other impurities with relative areas smaller then 0.1% were observed following the major peak.

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.8	0.09	0.5
2	9.0	1.00	100
3	11.1	1.23	0.2
4	12.1	1.34	1.1
5	17.2	1.91	0.1

F. **Conclusions:** Spectroscopy confirmed the identity of the material. Titration indicated an approximate purity of 97.5%. Gas chromatography indicated a maximum of seven impurities, each having individual relative areas greater than 0.1%; the total relative area was 2.3%. Spectroscopic and chromatographic data indicated that this batch was very similiar to lot no. DM113077.

II. Identification and Quantitation of an Impurity in Dimethyl Hydrogen Phosphite

A. Introduction

An impurity peak was detected in this batch of dimethyl hydrogen phosphite during the previous analysis. The impurity peak was observed by packed column gas chromatography and was estimated at 1.1% relative to the major component. Analysis was conducted to identify and quantitate this impurity.

B. Experimental Design

Packed column gas chromatography/mass spectrometry (GC/MS) full mass scan was used to identify the impurity in dimethyl hydrogen phosphite. The impurity was then quantitated against a specific standard by packed column gas chromatography by the internal standard method. The gas chromatography parameters used for this analysis duplicated those used in the previous analysis. The analyzed sample was taken from frozen reference material stored at Midwest Research Institute.

C. Impurity Identification

1. Sample Preparation

Solutions of dimethyl hydrogen phosphite (1.0% and 10.0%) were prepared volumetrically in high purity methylene chloride.

2. Instrumental System

Instrument: Finnigan MAT CH-4 mass spectrometer interfaced to a Varian 3700 gas chromatograph
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Carrier gas: Helium, approximately 30 ml/min
Inlet temperature: 200° C
Oven temperature program: 50°-170° C at 10° C/min with a 5 min initial hold
Mass spectrometer parameters

Temperatures:				
Transfer line:	250° C			
Helium separator:	250° C			
Ion source:	230° C			
Electron energy:	70 eV			
Emission current:	40 µA			
Accelerator voltage:	2.2 kV			
Electron multiplier voltage:	2,200V			
Resolution:	370			
Data type:	Exponential centroid			
Scan range:	0-600 scans			
Mass range:	10-280 amu			
Scan times:	Up:	1.75	Top:	0.05
	Down:	0.05	Bottom:	0.70

3. Results

The impurity was identified from the mass spectrum as trimethyl phosphate. The data are tabulated below (only m/z with relative abundance counts greater than 0.1% of the base peak are included). The identity of the impurity as trimethyl phosphate was confirmed by comparison of the observed mass spectrum to a literature reference of the compound (The Eight Peak Index of Mass Spectra, 1980).

The impurity that eluted after the major component is illustrated on the reconstructed ion current chromatogram (Figure 9). Mass spectra of dimethyl hydrogen phosphite and the trimethyl phosphate impurity are presented in Figures 10 and 11, respectively.

Mass (m/z)	Relative Abundance (percent of base peak)	Mass (m/z)	Relative Abundance (percent of base peak)
14	0.58	80	39.77
15	36.53	81	1.40
16	0.44	82	0.46
19	0.14	83	0.13
29	6.93	86	3.83
30	1.50	87	3.66
31	9.21	88	0.57
33	0.62	89	0.23
44	0.24	90	0.12
45	2.12	92	0.23
47	12.13	93	2.39
48	1.85	94	0.32
49	1.37	95	36.20
50	0.32	96	0.74
57	2.13	97	0.75
58	5.32	98	0.10
59	1.01	105	0.14
60	0.21	106	0.20
61	0.23	107	0.21
62	0.38	108	0.34
63	0.52	109	56.57
64	0.61	110	100.00
65	5.86	111	4.58
66	0.51	112	1.04
67	0.16	139	1.03
77	1.48	140	24.72
78	1.03	141	0.93
79	50.46	142	0.19

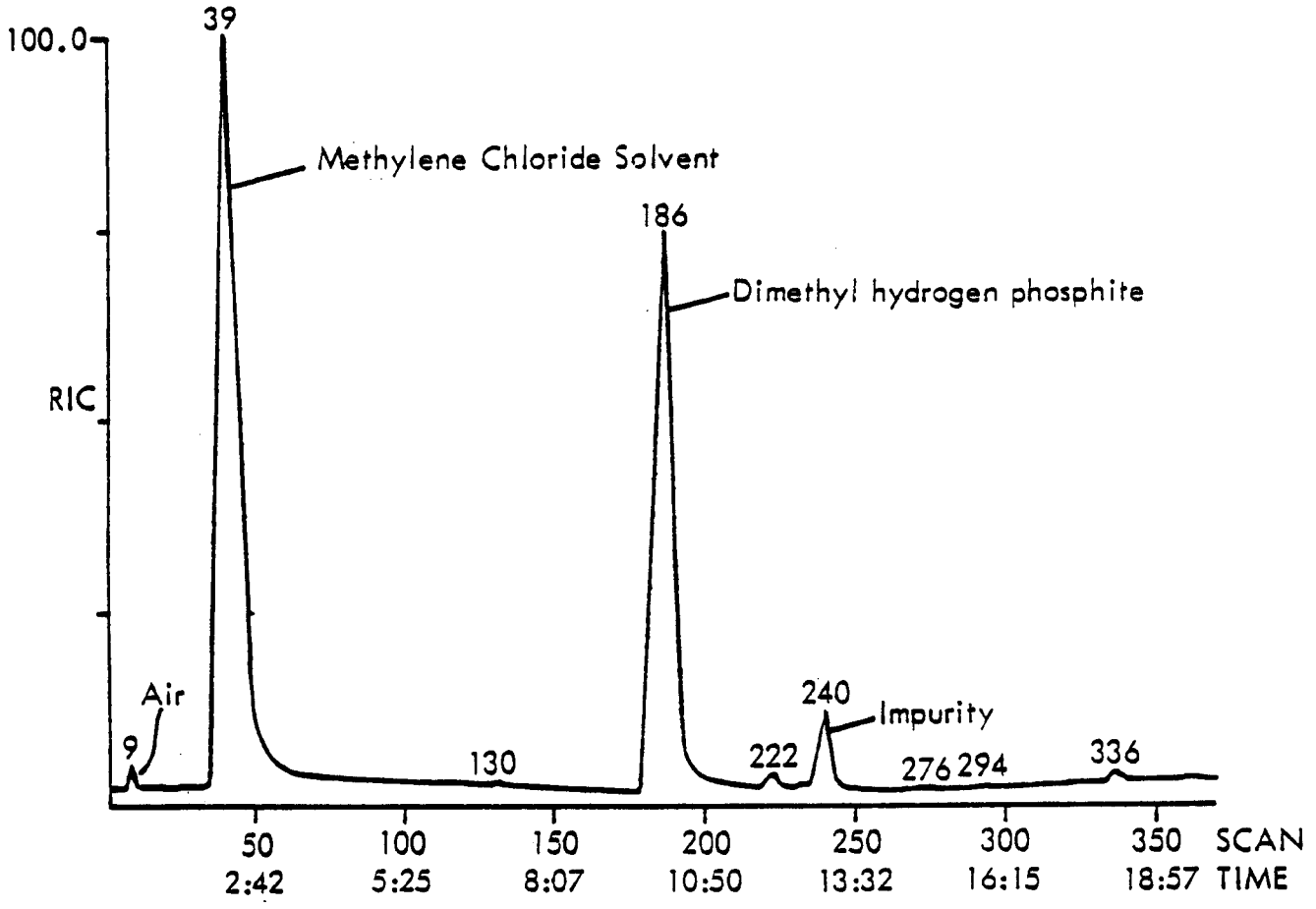

FIGURE 9. RECONSTRUCTED ION CURRENT CHROMATOGRAM FROM THE FULL MASS SCAN GC/MS ANALYSIS OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. KC031247)

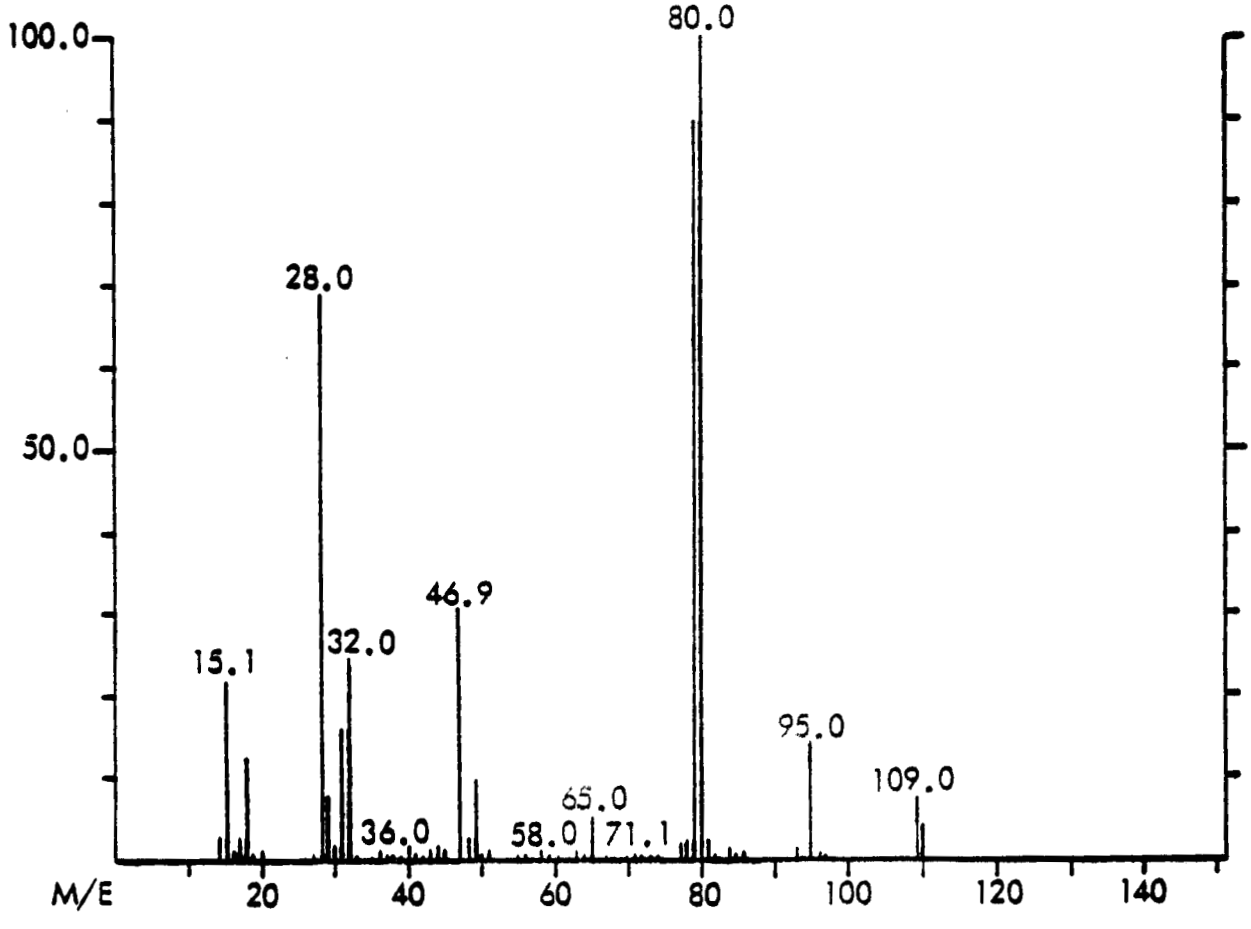

FIGURE 10. MASS SPECTRUM OF DIMETHYL HYDROGEN PHOSPHITE (LOT NO. KC031247)

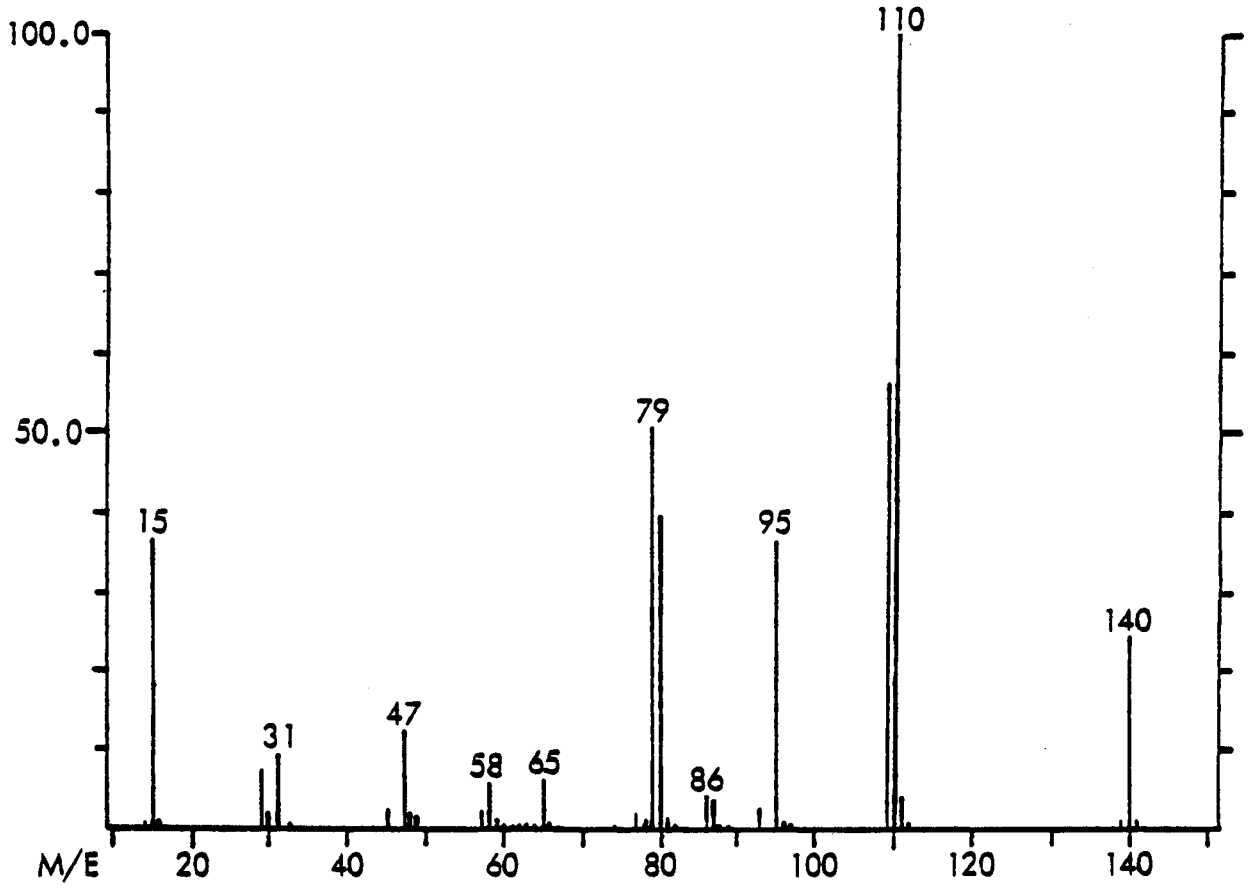

FIGURE 11. MASS SPECTRUM OF TRIMETHYL PHOSPHATE--DIMETHYL HYDROGEN PHOSPHITE IMPURITY (LOT NO. KC031247)

D. Impurity Quantitation

1. Sample Preparation

A 10.0% solution of dimethyl hydrogen phosphite containing 0.1% tripropyl phosphate internal standard was prepared volumetrically in high purity methylene chloride. Solutions of trimethyl phosphate standard (trimethyl phosphate, Aldrich Chemical Co., greater than 99% pure) (0.05%, 0.1%, and 0.2%), containing 0.1% tripropyl phosphate internal standard, also were prepared volumetrically with methylene chloride solvent.

2. Instrumental System

Instrument: Varian Vista 6000 with AutoSampler
Detector: Flame ionization
Column: 20% SP-2100/0.1 Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Carrier gas: Nitrogen, 70 ml/min
Inlet temperature: 200° C
Detector temperature: 250° C
Column oven temperature: 50°-170° C at 10° C/min with a 5 min initial hold

3. Results

The concentration of trimethyl phosphate in dimethyl hydrogen phosphite was 0.99% ± 0.04(δ)% by volume (n = 2).

The impurity peak in the dimethyl hydrogen phosphite had a retention time of 10.8 minutes, which coincided with that of the trimethyl phosphate standards. Additionally, the impurity peak was enhanced when the dimethyl hydrogen phosphite sample was spiked with a trimethyl phosphate standard.

Retention Times:
Trimethyl phosphate: 10.8 min
Internal standard: 19.9 min

The gas chromatographic profile obtained for this analysis was consistent with the reconstructed ion current chromatogram obtained by GC/MS analysis.

4. Conclusions

The impurity observed by GC during the original analysis of this batch of chemical was identified as trimethyl phosphate by GC/MS. The impurity was quantitated at 0.99% ± 0.04(δ)% (v/v) against a specific standard by GC.

III. Reanalysis of Bulk Material Performed by the Testing Laboratory

A. Analytical Methods

1. Gas Chromatography:

Instrument: Hewlett Packard 5880 or 5840A with 7672 Autosampler
Detector: Flame ionization
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, silanized glass
Detector temperature: 270° C
Inlet temperature: 200° C
Temperature program: 50° C for 5 min; 50°-200° C at 10° C/min; 200° C for 5 min
Carrier gas: Nitrogen
Carrier flow rate: 40 ml/min
Sample injection: 1 µl each of neat, 1.0% and 0.5% dimethyl hydrogen phosphite in methylene chloride to check for column and/or detector overload.

2. Infrared:

Instrument: Perkin-Elmer model 398, 1457, or 283B
Cell: Neat liquid between sodium chloride or potassium bromide plates

B. Results

1. Gas Chromatography:

Percent purity of dimethyl hydrogen phosphite

Date	Reference	Bulk
12/79	--	97.8
02/80	95.2	99.1
06/80	98.2	98.0
10/80	100	100
02/81	99.0	99.0
06/81	99.0	99.0
10/81	98.6	97.5
02/82	99.6	99.4
04/82	91.7	99.2

2. Infrared:

All spectra were consistent with those supplied by the analytical testing laboratory.

C. Conclusion:

No significant degradation of the test material occurred during the studies.

IV. Heat Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Dimethyl hydrogen phosphite samples were stored for 2 weeks at −20°, 5°, 25°, and 60° C in glass tubes with Teflon®-lined lids.

B. Analytical Method: Samples were analyzed by gas chromatography with the following system:

Instrument: Varian 3700 auto sampler
Column: 10% Carbowax 20M-TPA on 80/100 Chromasorb W(AW), 1.8 m × 4 mm ID, glass
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 310° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 140° C, isothermal
Retention time of major component: 3.0 min
Retention time of internal standard: 7.2 min
Sample injected: Solutions of 0.4% dimethyl hydrogen phosphite in methylene chloride containing 0.4% triethylphosphate internal standard were injected. The sample peak areas were compared with internal standard peak areas. The results were compared with the values obtained for the −20° C sample.

C. Results:

Storage Temperature	Percent Recovery
−20° C	100.0 ± 3.2
5° C	101.5 ± 3.2
25° C	99.8 ± 3.2
60° C	100.1 ± 3.2

D. Conclusion: Dimethyl hydrogen phosphite is stable as the bulk chemical when stored for 2 weeks at temperatures up to 60° C.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX H. PREPARATION AND CHARACTERIZATION

I. Sample Preparation and Storage: A stock solution was prepared by weighing 0.5098 ± 0.0001 g of dimethyl hydrogen phosphite into a 50-ml volumetric flask and diluting to the mark with corn oil, swirling occasionally. The solution then was manually shaken for 30 sec and placed in an ultrasonic vibratory bath for 5 min. As soon as the solution had been prepared, two accurately weighed 1.6-g aliquots were removed and sealed in separate 8.5-ml septum vials (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Biomedical Products, Inc.; aluminum crimp seals from Wheaton Scientific Company, Inc.), for use as initial, or zero-time, samples. The rest of the stock solution was stored at room temperature (25° C), and duplicate 1.6-g aliquots were removed for analysis after 1, 2, 6, and 7 days.

II. Sample Extraction and Analysis: Extracting solvent containing an internal reference standard was prepared by weighing 0.1477 ± 0.0001 g of triethylphosphate into a 50-ml volumetric flask and diluting to the mark with absolute methanol. Concentration of the reference standard is 2.954 ± 0.001 mg/ml.

To extract each sample aliquot, the septum vial was opened, 4.0 ml of the extracting solvent was added by volumetric pipette, and the vial was immediately resealed. The corn oil/methanol mixture was shaken by hand for 15 sec, agitated on a vortex mixer for 1 min, and placed in an ultrasonic vibratory bath for 2 min. The two phases were allowed to separate overnight, and 5-µl aliquots of the methanol layer were analyzed by the gas chromatographic system outlined below.

Instrument: Bendix 2500 with Heath chart recorder
Column: 10% Carbowax 20M-TPA on 80/100 Chromasorb W (AW), 1.8 m × 4 mm ID, glass
Detection: Flame ionization
Inlet temperature: 170° C
Detector temperature: 225° C
Carrier gas: Nitrogen
Carrier flow rate: 40 ml/min
Oven temperature program: 130° C isothermal
Retention time of major component: 3.6 min
Retention time of internal standard: 10.3 min

III. Quality Control Protocols: Analyses were performed in duplicate with triethylphosphate as an internal reference standard. Recovery studies (zero-time samples) were performed in duplicate at the same concentration level as the test samples, both at the start and at the end of the 7-day period. Gas chromatographic linearity was determined with standard solutions in methanol at concentrations of 3.91, 2.95, and 1.96 mg/ml for the dimethyl hydrogen phosphite and 2.93, 1.94, and 1.00 mg/ml for the internal reference standard. The least-squares plot correlation coefficients were 0.9999 for the test chemical and 0.9946 for the internal reference (effectively 1.0, linear).

IV. Results:

Storage Time (days)	Average Percent (w/w) DMHP Found in DMHP/ Corn Oil Mixture (a,b,c)
1	1.03 ± 0.02
2	1.02 ± 0.02
6	1.01 ± 0.02
7	1.01 ± 0.02

(a) Mean ± standard instrumental deviation
(b) Zero-time recovery yield, 100% ± 2%
(c) Theoretical concentration of dimethyl hydrogen phosphite in corn oil, 1.020% ± 0.001%

V. Conclusion: Dimethyl hydrogen phosphite in corn oil solution at the 1% concentration is stable within experimental error when stored at room temperature (25° C) for 7 days.

APPENDIX I

ANALYSIS OF DOSE MIXTURES: METHODS

APPENDIX I. ANALYSIS: METHODS

I. Testing Laboratory

A. Standard Solution Preparations:

1. Prepare a stock dimethyl hydrogen phosphite solution by weighing approximately 1.25 g into a 25-ml volumetric flask and diluting to volume with control corn oil. Target concentration is 50 mg/ml corn oil. Shake well and place the volumetric flask in an incubator (37° C) for about 10 min (the temperature of the stock solution is 1°-2° C higher than the room temperature, but there is no change in the volume).

2. Use the standard from step 1 to prepare a set of five calibration standards in the range of 50-10 mg/ml by volumetric dilutions of stock standard with undosed corn oil (similarly warmed) into 50-ml centrifuge tubes. Total volume should be 1.00 ml.

3. Prepare extractant with internal standard triethylphosphate in methanol to give a final concentration of 6 mg/ml.

B. Preparation of Gavage Solutions for Assay:

1. Together with standard solutions and control corn oil, incubate the samples to be assayed at 37° C for 10 minutes. Immediately prior to pipetting, mix each sample by vigorous shaking to form a uniformly homogeneous emulsion.

2. Using SMI pipettes, transfer in duplicate 1.0 ml aliquots of each sample (12.5 mg/ml and 25 mg/ml) into 50-ml centrifuge tubes. For the 50 mg/ml sample aliquot, transfer 500 µl in duplicate followed by 500 µl of undosed corn oil.

C. Extraction of Samples:

Add 5.00 ml of extractant to each centrifuge tube, seal, and shake for 10 min in a shaker box. Centrifuge at 1000 rpm for 10 min, and prepare aliquots of the methanol extract for gas chromatographic analysis.

D. Gas Chromatographic Conditions:

Instrument: HP 5880A with 7672A ALS
Detector: Flame ionization
Column: 10% Carbowax 20M TPA on Chromasorb W(AW), 1.8 m × 2 mm ID, silanized glass
Detector temperature: 225° C
Inlet temperature: 175° C
Temperature program: 130° C, isothermal
Carrier gas: Nitrogen
Flow rate: 40 ml/min.
Retention times: Dimethyl hydrogen phosphite, 2.6 min; triethylphosphate, 7.0 min

II. Analytical Chemistry Laboratory

A. Preparation of Standard Spiked Corn Oil : Two working standard solutions of dimethyl hydrogen phosphite in methanol were prepared independently at concentrations of 6.79 and 4.61 mg/ml. These solutions were diluted with methanol to concentrations of 3.40, 2.30, 1.70, and 1.15 mg/ml. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. The spiked corn oil mixtures and the corn oil blank were extracted immediately and were analyzed by the procedure described below.

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

C. Analysis: The vials were sealed (vial seals were Microsep F-138 gas chromatography septa with Teflon® film facing available from Canton Biomedical Products, Inc., Boulder, CO; the aluminum crimp seals and vials were available from Wheaton Scientific Co., Inc., Millville, NJ), vigorously agitated for 10 sec on a vortex mixer, and then shaken at maximum stroke for 15 min on a Burrell, Model 75, Wrist-Action® shaker. After the extraction, mixtures were centrifuged for 3 min, a 5-ml aliquot of the upper methanol layer from each vial was combined with 5 ml of internal standard solution (triethylphosphate in methanol, 7.5 mg/ml). The solutions were thoroughly mixed, and the dimethyl hydrogen phosphite content of each solution was determined by the gas chromatography system described below.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 10% Carbowax 20M TPA on 80/100 Chromosorb W(AW), 1.8 m × 2 mm ID, silanized glass
Detection: Flame ionization
Detector temperature: 230° C
Inlet temperature: 180° C
Temperature program: 120° C isothermal
Carrier gas: Nitrogen
Flow rate: 30 ml/min
Volume of solution injected: 3 µl
Retention times:
(1) Dimethyl hydrogen phosphite: 4.6 min
(2) Triethylphosphate:13.5 min

The total amount of dimethyl hydrogen phosphite in the referee corn oil samples was 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.

D. **Quality Assurance Measures:** The dosed referee corn oil sample was analyzed in triplicate, and the corn oil blank sample was analyzed once. Individually spiked portions of undosed corn oil (six concentrations) prepared from two independently weighed standards were used for obtaining standard curve data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

APPENDIX J

ANALYSES OF DOSE MIXTURES: DATA

TABLE J1. ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Date Mixed	Concentration of Dimethyl Hydrogen Phosphite in Corn Oil for Target Concentration (mg/ml) (a)		
	12.5 mg/ml	25 mg/ml	50 mg/ml
03/19/80	12.4	24.9	52.2
(b) 05/14/80		25.5	48.7
(c) 05/14/80	11.2	23.5	47.0
(b) 07/09/80		26.2	51.3
(c) 07/09/80	11.6	23.4	47.3
09/03/80	13.0	26.0	51.0
10/29/80	13.4	26.0	53.0
12/24/80	(d) 14.3	26.6	50.9
03/04/81	13.7	26.9	53.5
04/15/81	12.8	25.0	51.1
06/10/81	(d) 16.5	(d) 29.1	(d) 59.2
06/12/81	(d,e) 15.2	(d,e) 32.0	(d,e) 64.5
06/15/81	(e) 12.3	(e) 24.6	(e) 49.2
08/05/81	12.6	25.0	51.2
09/30/81	12.5	26.2	52.5
11/24/81	13.1	27.3	53.6
01/20/82	12.0	(d) 27.6	(d) 55.7
01/25/82		(e) 26.8	(e) 53.9
03/17/82	11.3	25.4	48.9
Mean (mg/ml)	12.9	25.9	51.7
Standard deviation	1.37	1.46	3.08
Coefficient of variation (percent)	10.6	5.6	6.0
Range (mg/ml)	11.2-16.5	23.4-29.1	47.0-59.2
Number of samples (f)	14	16	16

(a) The data presented are the results of duplicate analyses.
(b) Mice only
(c) Rats only
(d) Differs more than 10% from target value
(e) Remix
(f) Remixes not included in statistics so as to provide a measure of the overall accuracy of dose preparation

TABLE J2. REFEREE SAMPLE DATA IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Testing Laboratory	Referee Laboratory
5/14/80	12.5	11.20	12.28
10/29/80	12.5	13.40	12.54
6/10/81	50.0	59.15	49.80
11/24/81	12.5	13.15	12.50
3/17/82	25.0	25.30	24.90

APPENDIX K

GENETIC TOXICOLOGY OF

DIMETHYL HYDROGEN PHOSPHITE

TABLE K1. MUTAGENICITY OF DIMETHYL HYDROGEN PHOSPHITE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a)		
		−S9	+S9 (rat)	+S9 (hamster)
TA100	0	149 ± 5.4	197 ± 8.4	110 ± 6.1
	100	152 ± 11.5	170 ± 4.4	92 ± 3.3
	333	156 ± 9.8	186 ± 17.7	112 ± 6.2
	1,000	151 ± 6.5	189 ± 13.3	110 ± 4.3
	3,333	179 ± 9.6	199 ± 5.9	84 ± 13.8
	10,000	168 ± 9.1	224 ± 3.6	Toxic
TA1535	0	26 ± 3.0	11 ± 1.7	13 ± 2.2
	100	34 ± 3.5	10 ± 3.0	13 ± 2.0
	333	33 ± 1.9	13 ± 1.5	11 ± 1.2
	1,000	32 ± 2.8	12 ± 2.0	12 ± 0.3
	3,333	32 ± 1.9	14 ± 4.1	13 ± 2.4
	10,000	26 ± 1.5	Toxic	Toxic
TA1537	0	16 ± 0.9	19 ± 1.5	22 ± 3.2
	100	14 ± 2.2	27 ± 1.9	27 ± 4.3
	333	13 ± 0.7	18 ± 2.4	19 ± 2.9
	1,000	18 ± 2.7	19 ± 4.2	25 ± 2.4
	3,333	14 ± 0.6	19 ± 2.6	24 ± 1.8
	10,000	11 ± 1.2	15 ± 0.9	17 ± 4.2
TA98	0	31 ± 3.2	39 ± 2.7	43 ± 4.2
	100	35 ± 2.6	35 ± 2.1	36 ± 8.5
	333	33 ± 1.8	36 ± 2.5	39 ± 4.3
	1,000	37 ± 4.4	26 ± 6.0	31 ± 3.5
	3,333	37 ± 3.2	34 ± 1.9	29 ± 6.1
	10,000	42 ± 5.9	Toxic	Toxic

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (water) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 h (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE K2. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY DIMETHYL HYDROGEN PHOSPHITE

Route of Exposure	Dose (ppm)	No. of Lethals/No. of X Chromosomes Tested (a)			
		Mating 1	Mating 2	Mating 3	Total (percent)
Feeding	0	2/1,124	0/300	0/173	2/1,597
		0/1,789	1/1,461	1/1,265	2/4,515
		0/1,200	1/937	0/567	1/2,704
					5/8,816 (0.06)
	650	0/959	0/474	0/243	0/1,676
		2/1,156	0/1,150	1/965	3/3,271
		0/397	1/264	0/13	1/674
					4/5,621 (0.07)
Injection	0	1/1,358	3/1,360	6/1,349	10/4,067
		1/1,118	1/1,028	0/846	2/2,992
					12/7,059 (0.17)
	1,500	1/1,400	0/1,360	1/1,333	2/4,093
		1/798	0/733	3/698	4/2,229
					6/6,322 (0.09)

(a) The sex-linked recessive lethal assay was performed essentially as described by Abrahamson and Lewis (1971). Exposure by feeding was done by allowing 24-h-old Canton-S males to feed for 3 d on a solution of the test chemical dissolved in 5% sucrose. Exposure by injection was done by injecting 72-h-old adult males at the base of the halteres with enough of the test chemical dissolved in 0.7% sodium chloride to distend the abdomen (approximately 0.3 µl). Injected flies were allowed to recover for 24 h before being mated. Exposed males were mated to three *Basc* females for 3 d and given fresh females at 2-d intervals to produce three broods of 3, 2, and 2 d, after which the parents were discarded. F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental males were kept together to identify clusters; none were found. After 17 d, presumptive lethals were identified as vials containing no wild-type males; these were retested.

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. 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 were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. Sera from vehicle controls in the 13-week studies were also collected. The following tests were 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 (ectromelia virus)	M.Ad. (mouse adenovirus) MHV (mouse hepatitis virus) Sendai LCM (lymphocytic choriomeningitis virus)	MHV (24 mo.)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus)	RCV (rat coronavirus) Sendai	

II. Results

Results are presented in Tables L1 and L2.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

	No. of Animals	Positive Serologic Reaction for
RATS		
	2/10	RCV
	10/10	PVM
	10/10	Sendai
MICE		
	3/10	PVM
	10/10	Sendai

(a) Blood samples were taken from vehicle control animals (5/sex) just before the animals were killed.

TABLE L2. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL HYDROGEN PHOSPHITE (a)

	Interval	No. of Animals	Positive Serologic Reaction for
RATS			
	6 months	10	None positive
	12 months	10	None positive
	18 months	10	None positive
	24 months	10	None positive
MICE			
	6 months	10	None positive
	12 months	1/10	MVM
	18 months	10	None positive
	24 months	6/10	MHV

(a) Blood samples were taken from sentinel animals (5/sex) at 6, 12, and 18 months after the start of dosing and from the vehicle control animals (5/sex) just before they were killed. The samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screeening Program.

APPENDIX M

INGREDIENTS, NUTRIENT COMPOSITION, AND 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 #16 before mixing.

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}	4000 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)	24.14 ± 0.88	22.7-25.1	24
Crude fat (percent)	4.77 ± 0.34	4.1-5.4	24
Crude fiber (percent)	3.31 ± 0.50	1.4-4.3	24
Ash (percent)	6.67 ± 0.49	5.83-7.43	24
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} (ppm)	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
Essential Fatty Acids			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Essential Amino Acids			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.75	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

(a) One or two of the analyzed feed batches came from diet manufactured in January and/or April 1983.
(b) One batch (7/22/81) was 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)	0.11 ± 0.07	(a) <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)	7.17 ± 3.66	(e) <0.1-13.0	24
Nitrite nitrogen (ppm) (d)	1.88 ± 1.58	(e) <0.1-6.9	24
BHA (ppm) (f)	4.39 ± 3.72	(g) <0.4-13.0	24
BHT (ppm) (f)	2.67 ± 1.50	0.8-5.9	24
Aerobic plate count (CFU/g)	45,008 ± 33,225	5500-120000	24
Coliform (MPN/g) (d)	(h) 36.4 ± 52.5	<3-240	23
	(i) 125 ± 304	<3-1100	24
E. coli (MPN/g)	(j) <3		24
Total nitrosamines (ppb)	7.16 ± 6.92	(k) 0.8-24.5	21
	29.36 ± 64.76	(l) 0.8-273	24
N-Nitrosodimethylamine (ppb)	5.54 ± 6.03	(k) 0.8-20.0	21
	27.55 ± 64.41	(l) 0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.34 ± 0.93	0-3.5	24
Pesticides (ppm)			
Alpha BHC (m)	(b) <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
HCB	(b) <0.01		24
Mirex	(b) <0.01		24
Methoxychlor	(b) <0.05	(n) 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) <0.01	(n) 0.2 (4/27/81)	24
Methyl parathion	(b) <0.02		24
Ethyl parathion	(a) <0.02		24
Malathion	0.09 ± 0.07	(o) <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 less than 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) Excludes one very high value of 1100 obtained in the batch produced on 12/16/80
(i) Includes one very high value of 1100 obtained in the batch produced on 12/16/80
(j) All values were <3 MPN/g; MPN = most probable number
(k) All values are corrected for percent recovery; excludes 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.
(l) All values are corrected for percent recovery; includes 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.
(m) BHC is hexachlorocyclohexane or benzene hexachloride.
(n) One value above the detection limit (noted in the range column) was obtained on this date.
(o) Twelve batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and tables of the NTP Technical Report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite in F344/N rats and B6C3F$_1$ mice were examined during the period February to May 1984 for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted by Argus Research Laboratories and NTP personnel. The following persons were audit team members: Dr. E. Feussner, Dr. P. Ference, Dr. J. Goeke, Mr. J. Hills, Dr. R. Long, and Ms. C. Veigle. The 2-year studies in rats and mice were conducted between March 1980 and April 1982 at Litton Bionetics, Inc.

The full report of the audit is on file at the NTP Archives, Research Triangle Park, North Carolina. The audit consisted of a review of the records for the in-life portion of the studies; a review of 100% of the chemistry data, including chemical characterization, bulk chemical analysis, and characterization of dose mixtures; and a review of the pathology data. All Individual Animal Data Records for rats and mice were reviewed for correlation of gross lesions and microscopic diagnosis. Ten percent of wet tissues (random samples) were reviewed for animal identification and untrimmed lesions. A complete slide/block match for both sexes of rats and mice in the high dose and control groups was performed.

This audit review revealed no major problems with the execution of the studies or with the collection or reporting of the experimental data. The chemistry information in the Technical Report accurately reflects the data. Animals were identified individually as well as by test group. Animal record identification was good with no discrepancies seen in rats. One animal identification discrepancy was seen in mice: The records of two low dose female mice in the same cage were interchanged. Untrimmed lesions were infrequent and did not involve target organs. There were no discrepancies involving correlation of gross lesions with microscopic diagnosis in target organs (male rats--lung and forestomach; female rats--lung and forestomach). Discrepancies involving correlation of gross lesions with microscopic diagnosis in other nontarget organs were infrequent and randomly distributed among dose groups. Slide/block match was good: Questionable matches were infrequent (5 out of a total of 3,677 slides). Other minor problems not mentioned here were considered not to affect the outcome of the studies. In conclusion, no data discrepancies were found that would influence the final interpretation of this experiment.

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