NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 417

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *p*-NITROPHENOL (CAS NO. 100-02-7) IN SWISS-WEBSTER MICE (DERMAL STUDIES)

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *p*-NITROPHENOL

(CAS NO. 100-02-7)

IN SWISS-WEBSTER MICE

(DERMAL STUDIES)

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

April 1993

NTP TR 417

NIH Publication No. 93-3148

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

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
S.L. Eustis, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
R.A. Griesemer, D.V.M., Ph.D.
J.K. Haseman, Ph.D.
R.D. Irwin, Ph.D.
G.N. Rao, D.V.M., Ph.D.
C.C. Shackelford, D.V.M., M.S., Ph.D.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Hazleton Laboratories
Conducted studies, evaluated pathology findings

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

Experimental Pathology Laboratories, Inc.
Provided pathology quality assessment

J.F. Hardisty, D.V.M., Principal Investigator
S. Neuenschwander, M.S., D.V.M.

Integrated Laboratory Systems
Performed quality assurance audits

J.C. Bhandari, D.V.M., Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report (28 June 1990)

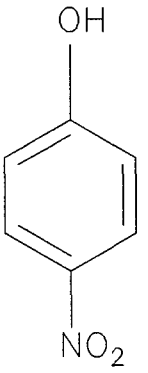
J.C. Seely, D.V.M., Chair
PATHCO, Inc.
M.R. Elwell, D.V.M., Ph.D.
National Toxicology Program
J. Everitt, D.V.M.
Chemical Industry Institute of Technology
M.P. Jokinen, D.V.M.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program

Biotechnical Services, Inc.
Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
G.F. Corley, D.V.M.
M.C. Hirrel, Ph.D.
K.D. Mencer, B.A.

CONTENTS

ABSTRACT



***p*-NITROPHENOL**

CAS No. 100-02-7

Chemical Formula: $C_6H_5NO_3$ Molecular Weight: 139.11

Synonyms: 4-hydroxynitrobenzene, *p*-hydroxynitrobenzene, 4-nitrophenol, paranitrophenol, PNP, Niphen

p-Nitrophenol is used in the production of acetaminophen, methyl and ethyl parathion insecticides, fungicides, and dyestuffs. Toxicology and carcinogenesis studies of *p*-nitrophenol (greater than 97% pure) were conducted by dermal application to male and female Swiss-Webster mice for 18 months. Dermal application was selected as the route of chemical administration because of possible skin absorption from *p*-nitrophenol-treated leather footwear. Genetic toxicology studies were conducted in *Salmonella typhimurium*, Chinese hamster ovary cells, and *Drosophila melanogaster*.

18-Month Studies

Groups of 60 Swiss-Webster mice of each sex received *p*-nitrophenol in acetone applied to the interscapular skin. Doses of 0, 40, 80, or 160 mg/kg *p*-nitrophenol were administered to mice 3 days per week for 78 weeks. At the end of the study, survival rates of mice receiving 0, 40, 80, or 160 mg/kg *p*-nitrophenol were 29/60, 17/60, 26/60, and 24/60 for males and 35/60, 26/60, 33/60, and 27/60 for females.

Deaths after 60 weeks were caused by generalized amyloidosis and secondary kidney failure. The severity of amyloidosis was similar among dosed and control animals. At the end of the study, the final mean body weights of the dosed groups of each sex were similar to those of the controls. No biologically significant lesions were observed that were related to the dermal administration of *p*-nitrophenol.

Genetic Toxicology

p-Nitrophenol was not mutagenic in *Salmonella typhimurium* (strains TA100, TA1535, TA1537, and TA98) with or without exogenous metabolic (S9) activation, or in germ cells of male *Drosophila melanogaster* administered *p*-nitrophenol in feed or by

injection. In Chinese hamster ovary cells, no induction of sister chromatid exchanges was observed with or without S9, but a significant increase in chromosomal aberrations occurred in trials conducted with S9.

CONCLUSIONS

Under the conditions of these 18-month dermal studies there was *no evidence of carcinogenic activity** in male or female Swiss-Webster mice receiving 40, 80, or 160 mg/kg *p*-nitrophenol.

---

*Explanation of Levels of Evidence of Carcinogenic Activity appears on page 8. A summary of Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

Summary of the 18-Month Carcinogenicity and Genetic Toxicology Studies of *p*-Nitrophenol

Variable	Male Swiss-Webster Mice	Female Swiss-Webster Mice
Doses	0, 40, 80, or 160 mg/kg in acetone applied to the interscapular skin at a dose volume of 100 μL	Same as male mice
Final body weights	Dosed groups similar to the controls	Dosed groups similar to the controls
18-Month survival rates	29/60, 17/60, 26/60, 24/60	35/60, 26/60, 33/60, 27/60
Nonneoplastic effects	None	None
Neoplastic effects	None	None
Levels of evidence of carcinogenic activity	No evidence	No evidence
Genetic toxicology		
Salmonella typhimurium gene mutations:	Negative with or without S9 metabolic activation in strains TA100, TA1535, TA1537, and TA98	
Sister chromatid exchange		
Chinese hamster ovary cells *in vitro*:	Negative with or without S9 metabolic activation	
Chromosomal aberration		
Chinese hamster ovary cells *in vitro*:	Negative without S9 metabolic activation; positive with S9 metabolic activation	
Sex-linked recessive lethal mutations		
Drosophila melanogaster:	Negative when administered in feed or by injection	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *p*-nitrophenol on July 9, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Subcommittee members have five major responsibilities:

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

Daniel S. Longnecker, M.D., Chair
Department of Pathology
Dartmouth Medical School
Hanover, NH

Paul T. Bailey, Ph.D., Principal Reviewer
Toxicology Division
Mobil Oil Corporation
Princeton, NJ

Louis S. Beliczky, M.S., M.P.H., Principal Reviewer
Department of Industrial Hygiene
United Rubber Workers International Union
Akron, OH

Gary P. Carlson, Ph.D.
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, D.V.M., Ph.D., Principal Reviewer
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, D.V.M.
Consultants in Veterinary Pathology
Murrysville, PA

Jay I. Goodman, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

David W. Hayden, D.V.M, Ph.D.
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

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

Barbara McKnight, Ph.D.
Department of Biostatistics
University of Washington
Seattle, WA

Ellen K. Silbergeld, Ph.D.*
University of Maryland Medical School
Baltimore, MD

Lauren Zeise, Ph.D.
Reproductive and Cancer Hazard Assessment Section
California Environmental Protection Agency
Berkeley, CA

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

Dr. C.C. Shackelford, NIEHS, introduced the toxicology and carcinogenesis studies of *p*-nitrophenol by discussing the uses of the chemical and the rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on the lack of compound-related neoplasms or nonneoplastic lesions in mice. The studies were terminated at 18 months because of reduced survival due to generalized amyloidosis and secondary kidney failure in both dosed and control animals. The proposed conclusions were *no evidence of carcinogenic activity* in male or female Swiss-Webster mice.

Dr. P.T. Bailey, a principal reviewer, agreed with the proposed conclusions. He questioned the sensitivity of Swiss-Webster mice to *p*-nitrophenol toxicity compared to that of other strains and whether parallels could be drawn between Swiss-Webster and other strains of mice used in classical carcinogenicity testing. Dr. Shackelford said there was no information on such studies in the literature. Dr. Bailey also asked whether clinical chemistry had been performed. Dr. Shackelford explained that at 65 weeks, when blood samples are normally taken for clinical chemistry, a large number of the animals were moribund and there were insufficient hematologic data to report.

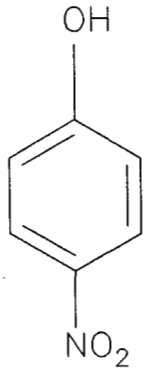
Dr. H. Davis, the second principal reviewer, agreed with the proposed conclusions. He questioned the rationale for using Swiss-Webster mice. Dr. R. Irwin, NIEHS, said that the U.S. Army specifically requested that the study be done in this strain.

Mr. L.S. Beliczky, the third principal reviewer, agreed with the proposed conclusions, although he considered the Swiss-Webster mouse a poor choice of animal, thus precluding any final judgment regarding either toxicity or carcinogenicity of *p*-nitrophenol. He said another study using a different strain of animal should be considered. Dr. S.L. Eustis, NIEHS, responded that the usual NTP rodent species, B6C3F$_1$ mouse and Fischer 344 rat, may not be the best strains to use for dermal carcinogenicity studies because they are relatively resistant to dermal carcinogenesis. He thought that other studies by another route in these strains would be more useful.

There was a lengthy discussion on the merits of exposure by the feed route versus dermal application and the point was made that when a chemical is given by one of these routes there is usually some degree of inadvertent exposure by the other route. Dr. R. Griesemer, NIEHS, commented that the design of the dermal study might be quite different depending on whether the concern was with skin as a target site or skin as a portal of entry.

Dr. Bailey moved that the Technical Report on *p*-nitrophenol be accepted with the conclusions as written for male and female Swiss-Webster mice, *no evidence of carcinogenic activity.* Dr. Davis seconded the motion, which was accepted unanimously with 10 votes.

INTRODUCTION



***p*-NITROPHENOL**

CAS No. 100-02-7

Chemical Formula: $C_6H_5NO_3$ Molecular Weight: 139.11

Synonyms: 4-hydroxynitrobenzene, *p*-hydroxynitrobenzene, 4-nitrophenol, paranitrophenol, PNP, Niphen

PHYSICAL AND CHEMICAL PROPERTIES

p-Nitrophenol is a colorless to slightly yellow, odorless crystalline solid. The chemical has a sweet taste accompanied by a burning aftertaste. It is moderately soluble in cold water, freely soluble in alcohol, acetone, ether, and chloroform, and soluble in solutions of fixed alkali hydroxides and carbonates (*Merck Index*, 1983). *p*-Nitrophenol is one of three mononitrophenol isomers; the other two isomers are *o*-nitrophenol and *m*-nitrophenol.

USE, PRODUCTION, EXPOSURE, AND METABOLISM

Mononitrophenols are used extensively in the production of dyes, pigments, pharmaceuticals, rubber, wood preservatives, photographic chemicals, and pesticides. Of the three mononitrophenol isomers, *p*-nitrophenol has the highest production volume and the greatest potential as an environmental pollutant. Prior to the late 1970's, approximately 87% of its production was used in the manufacture of the insecticides methyl and ethyl parathion. The primary use of *p*-nitrophenol, however, has shifted from the manufacture of parathion insecticides to acetaminophen (*N*-acetyl-*p*-aminophenol or APAP). In 1987 an estimated 46 million pounds of *p*-nitrophenol were produced annually. Of this amount, 55% was used to manufacture APAP, 35% was exported, and the remaining 10% went into leather tanning, dyestuffs, oxydianiline, and other miscellaneous uses (Kavaler, 1987). Atmospheric pollution with *p*-nitrophenol results from benzene emissions during oil refining and pesticide manufacturing, which produce trace amounts of *p*-nitrophenol from the photochemical reaction of benzene with nitrogen dioxide (Nojma *et al.*, 1983). Photodegradation products of *p*-nitrophenol-based compounds are also likely exposure sources.

Human exposure to *p*-nitrophenol is most likely to occur from inhalation. However, ingestion and direct skin contact are also possible, especially from *p*-nitrophenol-based fungicides. These fungicides are commonly used to prevent fungal infections of the foot

and have been used extensively in the manufacture of footwear issued to U.S. Army personnel (Angerhofer, 1985). From a survey conducted from 1981 to 1983, NIOSH estimated that 2,154 health services workers (1,552 females) were potentially exposed to *p*-nitrophenol in the United States (NIOSH, 1990). As benzyl derivatives, most phenols, especially di- and tri-hydroxy phenols, are readily absorbed through the skin; however, less polar derivatives, such as benzene or toluene, are not absorbed as readily by the skin (Sittig, 1985).

p-Nitrophenol is metabolized, primarily in the liver, into conjugated glucuronide and sulfate ester forms, which are the forms of *p*-nitrophenol excreted in urine by man and other animals (USEPA, 1980). Based on the rapid urinary elimination of mononitrophenols, the compounds may be restricted primarily to the blood and the urine following absorption in humans and animals. In rabbits, after oral administration of parathion, greater than 80% of the urinary *p*-nitrophenol was excreted as the glucuronide or sulfate ester conjugate within 6 hours (Peña-Egido *et al.*, 1988). *p*-Nitrophenol can also be metabolized, but in smaller amounts, to *p*-aminophenol by nitroreduction or to *p*-nitrocatechol by hydroxylation.

Exposure to *p*-nitrophenol can occur from the metabolism of parathion insecticides and other chemically related compounds, such as nitrobenzene with an estimated annual production of 900 million pounds, or through microbial metabolites. In studies with Sprague-Dawley rats and B6C3F$_1$ mice, nitrobenzene was metabolized to *p*-nitrophenol by aromatic hydroxylation and excreted in the urine as free compound, glucuronide, or sulfate ester conjugates. However, forms of excretion products vary with species and strains of animals (Rickert *et al.*, 1983).

TOXICITY

Although *p*-nitrophenol is the most toxic of the three mononitrophenol isomers, the toxicity of *p*-nitrophenol has only been partially characterized (USEPA, 1980). The oral LD_{50} for CF-1 mice is 470 mg/kg (range, 320 to 690 mg/kg) and for Sprague-Dawley rats it is 620 mg/kg (range, 450 to 850 mg/kg) (Vernot *et al.*, 1977). In general, the toxic effects of *p*-nitrophenol vary, with signs of hyperthermia, respiratory depression, methemoglobinemia, CNS depression, and central and peripheral vagal stimulation (Clayton and Clayton, 1981). Results from an acute and repeated dose inhalation study on *p*-nitrophenol sodium salts in male rats (doses of 0, 0.34, and 2.47 mg/L) revealed relatively low toxicity, i.e., methemoglobinemia, dark urine (methemoglobinuria), proteinuria, and elevated creatinine and SGOT levels. In addition, exposure to 2.47 mg/L caused elevated erythrocyte count, hemoglobin, and hematocrit. No compound-related histopathologic changes were noted (Smith *et al.*, 1988).

In humans the minimal toxic dose is extremely variable and the assessment of severity of toxicity is based on clinical findings (Rumack and Spoerke, 1991). Acute ingestion of as little as 1 g of pure phenol in adults has resulted in death. Toxicity in humans as a result of inhalation, ingestion, or absorption through intact skin causes headaches, drowsiness, nausea, and respiratory depression with blue color to the lips, ears, and fingernails (cyanosis), indicative of methemoglobinemia. Excretion in the urine of *p*-nitrophenol, a metabolite of the organophosphorus pesticides parathion, methyl parathion, O-ethyl O-*p*-nitrophenyl phenylphosphorothioic acid (EPN), and decathion, is a good indicator of human exposure to these compounds (USEPA, 1980).

The U.S. Army conducted a study in Sprague-Dawley rats to determine the effects, if any, of dermal application of *p*-nitrophenol in ethanol on prenatal rat activities from mating through lactation and in growth and development of offspring from conception through maturity (Angerhofer, 1985). Male and female rats were dosed with 50, 100, and 250 mg/kg *p*-nitrophenol in ethanol 5 days a week for up to 42 weeks. No significant differences in mating, pregnancy, behavior, and growth were found in parents or two subsequent generations when treated groups were compared with control groups. All rats receiving *p*-nitrophenol dermally experienced a dose-related pattern of skin irritation consisting of erythema, scaling, and crusting.

CARCINOGENICITY

p-Nitrophenol was studied in mice for dermal carcinogenic activity. Mice (strain unknown) received 20% *p*-nitrophenol in dioxane by dermal application, approximately 25 μL, twice weekly for 12 weeks

(Boutwell and Bosch, 1959). None of the survivors (30/31) had papillomas or other neoplasms, and no other histopathology was reported; however, the duration of the study may not have been long enough to establish evidence of carcinogenic activity.

Genetic Toxicology

p-Nitrophenol does not appear to be genotoxic. Positive genotoxic results have been occasionally reported for *p*-nitrophenol, but these studies were inadequate with respect to data presentation, study design, dose levels, endpoint evaluation, and/or information on chemical purity. Results from such studies are not cited in this Technical Report.

p-Nitrophenol did not cause bacteriophage induction in *Escherichia coli* (Ho and Ho, 1981); gene mutation in *Salmonella typhimurium* with or without metabolic activation (Buselmaier *et al.*, 1972; McCann *et al.*, 1975; Commoner, 1976; Haworth *et al.*, 1983; Suzuki *et al.*, 1983; Shimizu and Yano, 1986); or gene mutation in *Serratia marcescens* (Buselmaier *et al.*, 1972). No induced gene mutation (Amacher and Turner, 1982) or unscheduled DNA synthesis (Probst *et al.*, 1981) was observed in mammalian cells tested *in vitro* with *p*-nitrophenol. No induction of sex-linked recessive lethal mutations was reported in adult male *Drosophila melanogaster* administered *p*-nitrophenol in feed or by injection (Zimmering *et al.*, 1985).

p-Aminophenol is the only metabolite of *p*-nitrophenol for which genetic toxicity data are available. Like *p*-nitrophenol, *p*-aminophenol was negative for induction of gene mutations with or without metabolic activation in *E. coli* (Thompson *et al.*, 1983; DeFlora *et al.*, 1984b) and *S. typhimurium* (McCann *et al.*, 1975; Degawa *et al.*, 1979; Lavoie *et al.*, 1979; Thompson *et al.*, 1983; DeFlora *et al.*, 1984a,b; Matula *et al.*, 1984; Zeiger *et al.*, 1988). *p*-Aminophenol did not induce sex-linked recessive lethal mutations in adult male *D. melanogaster* when administered in feed or by injection but did induce somatic mutation and recombination (SMART test) in *D. melanogaster* larvae (Eiche *et al.*, 1990). In the SMART test, a positive result may also indicate chromosome breakage or aneuploidy, as well as some unknown epigenetic event. Since the endpoint scored is a phenotypic change rather than a genotypic change, the precise change induced by *p*-aminophenol cannot be determined.

p-Aminophenol has been reported to inhibit DNA synthesis and to alter DNA structure in EBV-transformed human lymphoblastoid cells (Hayward *et al.*, 1982). *p*-Aminophenol also caused gene mutation in mouse lymphoma L5178Y cells (Amacher and Turner, 1982; Oberly *et al.*, 1984) and induced sister chromatid exchanges in human lymphocytes *in vitro* (Takehisa and Kanaya, 1982).

Positive responses for induction of chromosomal aberrations in mouse bone marrow cells with *p*-aminophenol were reported (Mitra and Manna, 1971), but these data showed no dose response, and apparently no positive or negative controls were included. Positive results for *p*-aminophenol in mouse bone marrow micronucleus (MN) tests were reported in two abstracts (Wild *et al.*, 1981; Cliet *et al.*, 1989), but these contained no data for evaluation. Another study using the bone marrow MN test clearly demonstrated significant ($P<0.01$) increases in micronucleated polychromatic erythrocytes (PCE) following two intraperitoneal injections of either 218 or 436 mg/kg *p*-aminophenol (Wild *et al.*, 1980). These positive MN test results contrast with negative results reported for a rat bone marrow MN test following the administration of *p*-aminophenol by gavage with doses as large as 3,200 mg/kg (Hossack and Richardson, 1977).

Study Rationale

At the request of the USEPA, the U.S. Army nominated *p*-nitrophenol to the National Toxicology Program for testing because leather used in the manufacture of boots and shoes for Army and other military personnel (approximately 3 million pairs yearly) is treated with fungicides containing 7% *p*-nitrophenol. The risk of exposure was considered high enough to require dermal oncogenicity testing of *p*-nitrophenol. The Swiss-Webster strain of mouse was chosen because of its use in preliminary studies on *p*-nitrophenol begun by the U.S. Army. The route of administration selected for these studies on *p*-nitrophenol was dermal application.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *P*-NITROPHENOL

p-Nitrophenol, manufactured by E.I. duPont de Nemours & Company, Incorporated (Wilmington, DE), was obtained in one lot (lot number 730). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO).

The bulk chemical, a buff to tan-colored flaked solid, was identified as *p*-nitrophenol by its melting point and its infrared, ultraviolet, and nuclear magnetic resonance spectra (Figures E1 and E2). Purity was evaluated by elemental analysis, water analysis, titration of phenol and nitro groups, thin layer chromatography (TLC), and high performance liquid chromatography (HPLC). Purity was estimated at greater than 97%. No impurities were detected by either TLC or HPLC.

p-Nitrophenol was found to be stable in bulk form when stored for 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at 4° to 5° C. Throughout the studies, the study laboratory periodically monitored the stability of the bulk chemical by HPLC and ultraviolet spectroscopy (Appendix E).

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations of *p*-nitrophenol were prepared by mixing the appropriate amount of *p*-nitrophenol in acetone (Mallinckrodt; analytical reagent grade) (Table E1). Since the dosing volume was kept constant at 100 μL, the formulations and concentrations were changed over the course of the study to maintain the same dose per body weight. Dose formulations of *p*-nitrophenol were found to be stable by the analytical chemistry laboratory for at least 3 weeks at room temperature when protected from light. Once prepared, formulations were stored at −20° C in amber glass vials with Teflon®-lined caps until the week of dosing; thereafter, formulations were kept for 2 weeks at room temperature and protected from light.

Dose analyses of *p*-nitrophenol in acetone were performed at approximately 2-month intervals by the study laboratory using flame-ionization gas chromatography with *n*-undecanol as an internal standard (Appendix E). Dose formulations were within 10% of the desired concentrations throughout the studies. The study laboratory sent samples of the dose formulations to the analytical chemistry laboratory for referee analyses. Results of periodic analyses of the dose formulations conducted by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Table E3).

18-MONTH STUDIES

Study Design

Sixty male and 60 female Swiss-Webster mice received 0, 40, 80, or 160 mg/kg *p*-nitrophenol in 100 μL acetone applied directly to the interscapular skin three times per week (Monday, Wednesday, and Friday; excluding holidays) for 78 weeks. Once every week, fur in the area of the skin receiving the dose application was clipped. A summary of the experimental design for the 18-month dermal studies is presented in Table 1.

The doses selected for the 18-month studies were based on unpublished data from 13-week studies conducted at the Gulf South Research Institute, New Iberia, Louisiana (Appendix D). Based on the survival and histopathologic lesions in these 13-week studies, the doses selected for the 18-month dermal studies of *p*-nitrophenol were 0, 40, 80, and 160 mg/kg.

Source and Specification of Animals

Swiss-Webster (strain CFW/CR) mice were obtained from the Charles River Breeding Laboratories (Portage, MI). Mice were observed for 14 days

before the studies began and were 6 weeks old when the first dose was applied. Prior to treatment assignment, five mice of each sex were randomly sacrificed and examined for gross lesions and the presence of disease. Animal health and murine virus antibodies were monitored throughout the studies in mice assigned to the NTP Sentinel Animal Program (Appendix G).

Animal Maintenance

Mice were separated by sex, weighed, grouped by weight class, and then randomly assigned to cages, where they were housed individually throughout the studies. Cages were arranged vertically in racks by dose group. Once every 2 weeks, cages were relocated on the racks, and the cage racks were relocated within the animal room. Mice received food and water (Rockville, MD, city water supply system) *ad libitum*. Further details on animal maintenance are given in Table 1.

Clinical Examinations and Pathology

Mice were examined twice daily for mortality, changes in appearance or behavior, and signs of toxicologic or pharmacologic effects. Clinical findings were recorded weekly for the first 13 weeks, then at 4-week intervals thereafter until the end of the study. Body weights were recorded weekly for the first 12 weeks, then every 4 weeks until the end of the study. Complete necropsies were performed on all mice. During necropsy all organs and tissues were examined for gross lesions. Complete histopathologic examination was performed on all mice. Tissues selected for microscopic examination were preserved in 10% neutral buffered formalin. To prepare the tissue for microscopic examination, the preserved tissue was embedded in paraffin, sectioned 4 to 6 μm thick, and stained with hematoxylin and eosin. The tissues examined microscopically are listed in Table 1.

Pathology evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The laboratory animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated.

A quality assessment pathologist microscopically reviewed the lung from all male mice and the uterus and vagina from all female mice for accuracy and consistency of lesion diagnosis. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chair. After review of the pathology incidence tables, the original study pathology report, and the quality assessment pathology report, the PWG Chair selected 60 slides for review by the PWG. These slides included representative examples of proliferative lesions from the lungs of male mice and from the uterus of female mice as well as any lesions from organs for which there was disagreement in diagnosis between the study laboratory and quality assessment pathologist. The PWG included the quality assessment pathologist and others experienced in rodent toxicologic pathology who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). The final pathology data represent a consensus of contractor pathologists and the PWG. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were separated or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented graphically. Animals were censored from the survival analyses at the time they were found dead from other than natural causes. Animals dying from natural causes were not censored. Statistical analysis 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 to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, and B4 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3 and B3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with that lesion examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

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

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in Appendixes A and B. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals. Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm incidence; reported P values are one sided. The procedures described above were also used to evaluate selected nonneoplastic lesions. These methods are discussed further in Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

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

Quality Assurance Methods

The 18-month studies were conducted in compliance with FDA Good Laboratory Practice Regulations (CFR, part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits were conducted for completeness and accuracy of the pathology data, pathology specimens, and final pathology tables, as well as the Preliminary draft of this NTP Technical Report. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of *p*-nitrophenol was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium* (strains TA100, TA1535, TA1537, and TA98), sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, and sex-linked recessive lethal mutations in *Drosophila melanogaster*. The protocols for these studies and tabular presentations of the findings are given in Appendix C.

TABLE 1
Experimental Design and Materials and Methods in the Dermal Study of *p*-Nitrophenol

Study Laboratory
Hazleton Laboratories America, Inc. (Rockville, MD)

Strain and Species
Swiss-Webster (CFW/CR) mice

Animal Source
Charles River Breeding Laboratories (Portage, MI)

Observation Period Before Study Began
14 days

Average Age When Study Began
6 weeks

Average Age When Killed
85 weeks

Animals per Cage
1

Method of Animal Identification
Toe clip

Diet
NIH-07 diet (Zeigler Brothers, Gardners, PA), available *ad libitum*

Maximum Storage Time for Feed
120 days

Water
Tap water (Rockville, MD, city water supply), available *ad libitum*, in glass bottles with stainless steel sipper tubes (Lab Products, Garfield, NJ), changed twice weekly

Cages
Polycarbonate, solid bottom (Lab Products, Garfield, NJ), changed weekly

Bedding
BetaChips® hardwood laboratory bedding (Northeastern Products, Warrensburg, NY), changed weekly

Cage Filters
Nonwoven polyester fiber (Snow Filtration, Cincinnati, OH), placed over each row of cages on each rack, changed every 2 weeks

Animal Room Environment
Temperature: 20°-26° C
Relative humidity: 33%-77%
Fluorescent light: 12 hours/day
Room air changes: more than 15/hour

TABLE 1
Experimental Design and Materials and Methods in the Dermal Study of *p*-Nitrophenol (continued)

Dose Groups	0, 40, 80, 160 mg/kg in 100 μL acetone applied to the clipped interscapular skin
Size of Study Groups	60 males and 60 females
Date of First Dose	7 November 1984
Date of Last Dose	5 May 1986
Duration of Dosing	3 times weekly (Monday, Wednesday, and Friday; excluding holidays) for 78 weeks
Type and Frequency of Examinations	Examined twice daily; clinical findings recorded weekly for the first 13 weeks, then at 4-week intervals thereafter until the end of the study; weighed weekly for the first 12 weeks, then every 4 weeks until the end of the study
Necropsy	Complete necropsies were performed on all mice.
Histopathology	Complete histopathologic examination was performed on all mice. Tissues examined included adrenal gland (cortex, medulla), bone (including marrow), brain, epididymis, gallbladder, heart (females only), kidney, large intestine (cecum, females only; colon; rectum, males only), liver, lung, mammary gland (females only), mandibular lymph node, mediastinal lymph node (males only), mesenteric lymph node, mesentery, nose, ovary, pancreas (islets), parathyroid gland (females only), pituitary gland (pars distalis), prostate gland, salivary gland, skin (including interscapular region/site of application, tail), small intestine (duodenum, females only; jejunum; ileum), spleen, stomach (forestomach, glandular), testes, thymus, thyroid gland (females only), urinary bladder, and uterus. Tissues examined, if tissue masses and/or gross lesions were present, included ears, eyes, and harderian gland.

RESULTS

Survival

Survival of dosed female mice was similar to that of the controls as was that of males receiving 80 or 160 mg/kg. Survival of 40 mg/kg males was significantly lower than that of controls (Table 2), but the difference was not considered to be related to chemical administration. There were relatively few deaths during the first 60 weeks of the study, and thereafter, survival began to decrease abruptly for all dosed and control groups (Figure 1).

Body Weights and Clinical Findings

Mean body weights of dosed male and female mice were similar to those of the controls throughout the study (Tables 3 and 4 and Figure 2). At 60 weeks, some of the mice from all groups, including controls, began to appear emaciated and exhibited generalized edema of the head and other parts of the body. At necropsy, the abdominal and thoracic cavities of animals with edema were filled with a clear, watery fluid (ascites). The spleen and kidneys were enlarged and had a pale appearance on the cut surface. These animals had clinical evidence of anemia and hypoproteinemia which agreed with the histologic evidence of severe amyloid-associated kidney damage. Once these clinical signs of amyloidosis developed, death was imminent.

Pathology and Statistical Analyses of Results

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms are presented in Appendix A for male mice and Appendix B for female mice. No statistically significant or biologically noteworthy changes occurred in the incidences of nonneoplastic lesions at any site.

The overall incidence of benign and malignant neoplasms in this study was elevated in male mice in the low- and mid-dose groups (Table A3). However, this elevation in neoplasm incidence was not due to any one type of neoplasm and there was no significant dose-related trend for any neoplasms.

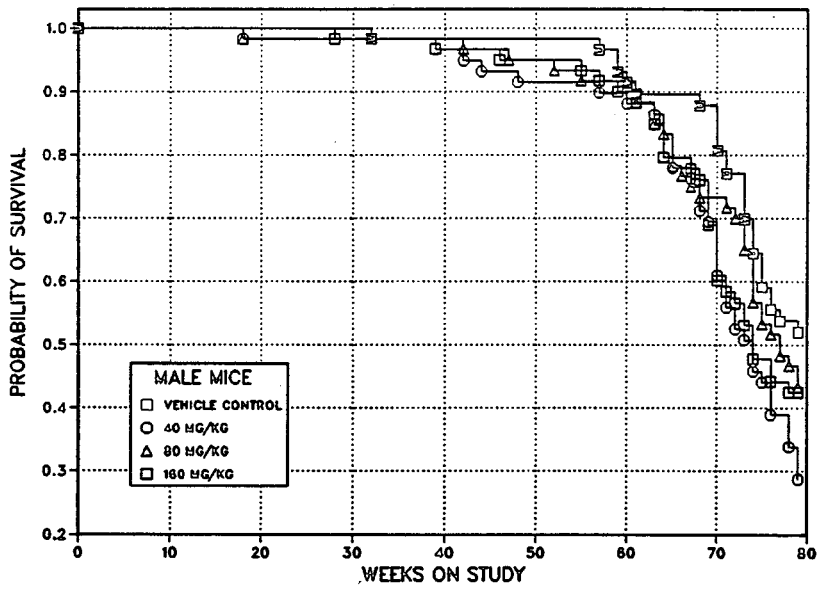
In male mice two neoplasms were observed at the site of chemical application: a keratoacanthoma in the 40 mg/kg dose group and a papilloma in the 80 mg/kg dose group (Table 5). No neoplasms were observed at the site of chemical application in female mice. Since there were no dose-related increases in these skin neoplasms they were not considered to be related to the administration of *p*-nitrophenol. No significant chemical-related nonneoplastic skin lesions were observed at the site of application or control site in mice of either sex during these studies.

Alveolar/bronchiolar adenomas (vehicle control, 4/60; 40 mg/kg, 11/58; 80 mg/kg, 12/60; 160 mg/kg, 6/60) and alveolar/bronchiolar adenomas or carcinomas (9/60, 20/58, 17/60, 11/60) were marginally increased in dosed males with the low-dose group being statistically significant ($P<0.05$). An increase in lung neoplasms in female mice was not observed (11/60, 9/60, 12/60, 11/60). The incidence of alveolar epithelial hyperplasia did not increase in dosed males (5/60, 1/58, 2/60, 2/60). Currently there is no information pertaining to historical control neoplasm incidences in Swiss-Webster mice. However, since the increases in lung neoplasms were not dose-related and alveolar epithelial hyperplasia was not increased in any of the treatment groups, these neoplasms were not considered to be related to *p*-nitrophenol administration.

TABLE 2
Survival of Mice in the 18-Month Dermal Studies of *p*-Nitrophenol

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Male				
Animals initially in study	60	60	60	60
Natural deaths	5	8	11	12
Moribund	22	34	23	21
Accidental deaths	4	1	0	3
Animals surviving to study termination	29	17	26	24
Percent probability of survival at end of study[a]	52	29	43	43
Mean survival days[b]	505	483	502	493
Survival P values[c]	P=0.498	P=0.013	P=0.387	P=0.186
Female				
Animals initially in study	60	60	60	60
Natural deaths	5	7	5	7
Moribund	20	27	22	25
Accidental deaths	0	0	0	1
Animals surviving to study termination	35	26	33	27
Percent probability of survival at end of study[a]	58	43	55	46
Mean survival days[b]	511	505	521	511
Survival P values[c]	P=0.614	P=0.203	P=0.990	P=0.386

[a] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[b] Mean of all deaths (uncensored, censored, terminal sacrifice)
[c] The entry under the "Vehicle Control" column is associated with the life table trend test (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972).



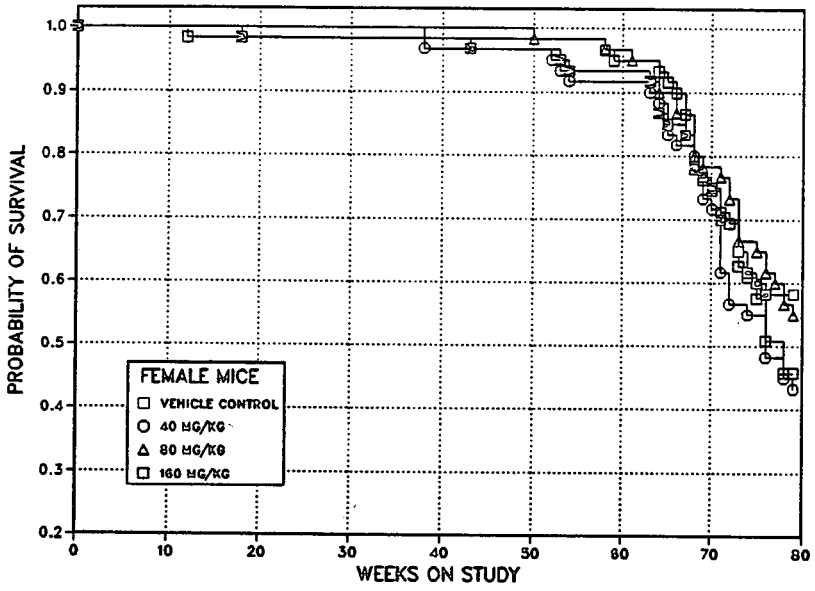


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Mice Administered *p*-Nitrophenol by Dermal Application for 18 Months

TABLE 3
Mean Body Weights and Survival of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol

Weeks on Study	Vehicle Control		40 mg/kg			80 mg/kg			160 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.6	60	24.8	101	60	25.0	102	60	24.8	101	60
2	26.1	60[a]	26.3	101	60	27.0	103	60[a]	26.4	101	60
3	27.9	60	27.7	99	60	28.5	102	60	28.1	101	60
4	28.6	60	28.1	98	60	29.0	101	60	28.5	100	60
5	29.5	60	29.2	99	60	29.6	100	60	29.1	99	60
6	29.1	60	28.7	99	60	29.2	100	60	28.9	99	60
7	30.2	60	30.1	100	60	30.9	102	60	30.2	100	60
8	30.7	60	30.6	100	59	31.1	101	60	30.5	99	60
9	31.0	60	31.1	100	59	32.0	103	60	31.3	101	60
10	30.8	60	31.0	101	59	31.9	104	60	31.6	103	60
11	31.5	60	31.7	101	59	32.5	103	60	31.8	101	60
12	31.6	60	31.9	101	59	32.7	104	60	31.7	100	60
16	33.8	60	33.8	100	59	34.4	102	60	33.8	100	60
20	34.6	59	34.7	100	58	35.4	102	59	34.8	101	60
24	35.1	59	35.3	101	58	36.0	103	59	35.5	101	60
28	35.8	59	36.0	101	58	36.6	102	59	36.3	101	59
32	35.8	58	36.0	101	58	36.8	103	59	36.1	101	59
36	36.7	58	36.7	100	58	37.3	102	59	36.7	100	59
40	36.6	58	36.3	99	58	36.9	101	59	36.7	100	58
44	37.1	58	36.7	99	55	37.3	101	58	37.3	101	58
48	37.7	58	37.4	99	54	38.4	102	57	37.8	100	57
52	37.7	57	37.6	100	54	38.3	102	56	38.0	101	57
56	37.9	57	37.6	99	54	38.1	101	55	37.8	100	56
60[a]	37.3	52	35.7	96	52	38.7	104	55	36.8	99	52
61[a]	37.0	50	37.7	102	52	36.3	98	53	37.8	102	51
64	38.1	50	38.0	100	47	38.6	101	50	38.0	100	46
68	38.2	49	37.7	99	42	38.5	101	44	37.5	98	43
72	36.5	43	36.4	100	31	36.7	101	42	36.1	99	32
76	36.9	31	35.6	97	23[a]	37.0	100	31	35.9	97	25
Terminal sacrifice		29			17			26			24
Mean for weeks											
1-13	29.3		29.3	100		30.0	102		29.4	100	
14-52	36.1		36.1	100		36.7	102		36.3	101	
53-76	37.4		37.0	99		37.7	101		37.1	99	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.

TABLE 4
Mean Body Weights and Survival of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol

Weeks on Study	Vehicle Control		40 mg/kg			80 mg/kg			160 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.2	60	20.1	100	60	20.2	100	60	20.0	99	60
2	21.3	60	21.1	99	60	21.5	101	60	21.1	99	60
3	22.2	60	22.3	101	60	22.4	101	60	22.4	101	60
4	22.6	60	22.5	100	60	22.5	100	60	22.4	99	60
5	23.5	60	23.3	99	60	23.3	99	60	23.4	100	60
6	23.3	60	23.1	99	60	23.2	100	60	23.0	99	60
7	23.9	60[a]	23.7	99	60	24.0	100	60	23.8	100	60
8	24.1	60	23.9	99	60	24.1	100	60	24.0	100	60
9	24.4	60	24.2	99	60	24.5	100	60	24.4	100	60
10	24.1	60	23.8	99	60	24.3	101	60	24.3	101	60
11	24.9	60	24.7	99	60	24.9	100	60	24.6	99	60
12	24.7	60	24.5	99	60	24.9	101	60	24.4	99	60
16	26.2	60	26.2	100	60	26.1	100	60	26.2	100	59
20	26.6	59	26.8	101	60	26.9	101	60	26.7	100	59
24	27.1	59	27.1	100	60	27.4	101	60	26.9	99	59
28	27.7	59	27.7	100	60	28.0	101	60	27.8	100	59
32	27.5	59	27.4	100	60	27.7	101	60	27.2	99	59
36	28.2	59	28.1	100	60	28.5	101	60	28.1	100	59
40	28.4	59	28.4	100	58	28.5	100	60	28.1	99	59
44	28.9	58	28.5	99	58	28.7	99	60	28.3	98	59
48	29.5	58	29.1	99	58	29.9	101	60	29.0	98	59
52	29.5	58	29.2	99	57	30.0	102	59	29.2	99	59
56	30.0	56	29.3	98	55	30.1	100	59	29.1	97	58
60[a]	29.1	56	29.6	102	55	28.9	99	58	28.9	99	56
61[a]	31.1	56	28.2	91	55	28.9	93	57	29.6	95	56
64	30.5	52	30.2	99	53	30.5	100	54	29.8	98	55
68	30.8	47	30.5	99	48	30.8	100	48	30.7	100	46
72	30.0	42	30.1	100	34	29.8	99	44	29.5	98	41
76	30.4	35	30.4	100	29	29.9	98	37	29.6	97	30
Terminal sacrifice		35			26			33			27
Mean for weeks											
1-13	23.3		23.1	99		23.3	100		23.2	100	
14-52	28.0		27.9	100		28.2	101		27.8	99	
53-76	30.3		29.8	98		29.8	98		29.6	98	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.

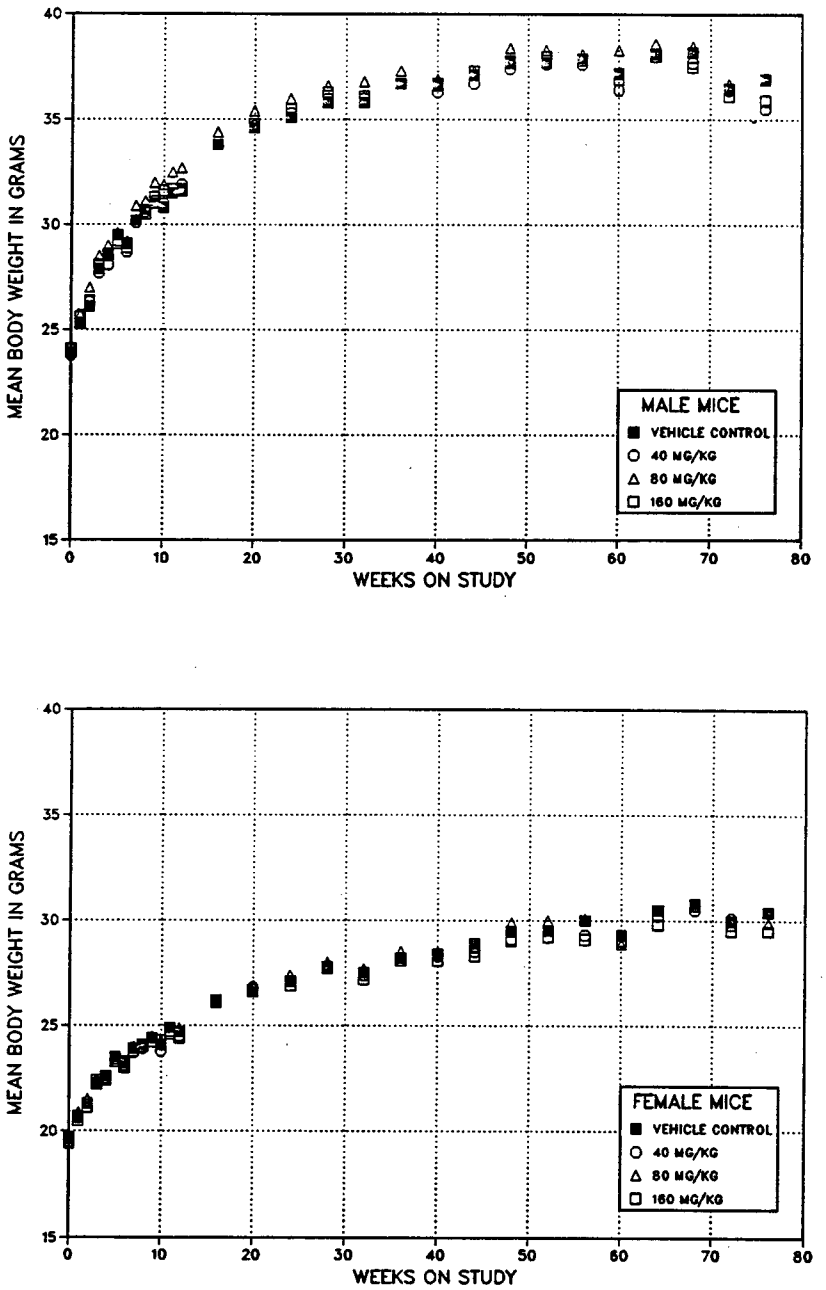


FIGURE 2
Growth Curves for Male and Female Mice Administered *p*-Nitrophenol by Dermal Application for 18 Months

TABLE 5
Selected Lesions of the Skin in the 18-Month Dermal Studies of *p*-Nitrophenol

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Male				
Skin, control site				
Inflammation, chronic	2/60	1/60	0/60	3/60
Skin, site of application				
Keratoacanthoma	0/60	1/60	0/60	0/60
Papilloma	0/60	0/60	0/60	1/60
Acanthosis	1/60	3/60	3/60	1/60
Hyperkeratosis	1/60	1/60	1/60	1/60
Ulcer	0/60	1/60	3/60	0/60
Inflammation, chronic	0/60	5/60	4/60	3/60
Female				
Skin, control site				
Hyperkeratosis	0/60	0/60	0/60	1/60
Inflammation, chronic	3/60	2/60	3/60	0/60
Skin, site of application				
Acanthosis	4/60	1/60	0/60	1/60
Hyperkeratosis	2/60	0/60	0/60	1/60
Ulcer	3/60	0/60	0/60	1/60
Inflammation, chronic	11/60	9/60	2/60	7/60

GENETIC TOXICOLOGY

p-Nitrophenol (10-3,333 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when preincubated in the absence or presence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table C1; Haworth *et al.*, 1983). A weakly positive response was observed in one trial with strain TA98 in the presence of hamster S9; this response could not be duplicated in the second trial.

In the cytogenetic tests with Chinese hamster ovary (CHO) cells, *p*-nitrophenol did not induce sister chromatid exchanges with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table C2). In the first trial conducted with S9, a weakly positive response was observed at the highest nonlethal dose tested (500 μg/mL), but this response could not be repeated in a second trial performed with higher doses of *p*-nitrophenol; therefore, the assay was concluded to be negative. *p*-Nitrophenol induced cell cycle delay which required harvest times to be extended for most cultures to ensure adequate numbers of cells for analysis. In the chromosomal aberration test with CHO cells, *p*-nitrophenol was negative in the absence of S9, but a significant increase in aberrations was observed in each of two trials with S9 at concentrations which induced cell cycle delay (Table C3). A reduced number of cells were scored at the higher dose levels in the chromosomal aberration test with S9 due to an increased number of aberrations per cell and because of a reduced population of scorable cells. A small reduction in cell confluence (indicative of slight toxicity) was noted at both the 1,750 and 2,000 μg/mL dose levels in the first trial with S9, yet induction of chromosomal aberrations occurred at the highest dose only. No reduction in confluence was noted in any of the doses in the second trial. *p*-Nitrophenol was negative for induction of sex-linked recessive lethal mutations in the germ cells of male *Drosophila melanogaster* when the chemical was administered in feed (up to 7,500 ppm) or by injection (up to 1,500 ppm) (Table C4; Zimmering *et al.*, 1985).

DISCUSSION AND CONCLUSIONS

p-Nitrophenol, a colorless to slightly yellow, odorless crystalline solid, is used primarily as a chemical intermediate in the production of the insecticides methyl and ethyl parathion as well as other pesticides. Additionally, a 7% solution of *p*-nitrophenol is used as a fungicide to treat footwear issued to all U.S. Army personnel for the prevention of foot infections. Since *p*-nitrophenol, a mononitrophenol isomer, may be metabolized or chemically reduced to a hydroxylamine intermediate that has potential carcinogenic activity, the U.S. Army nominated *p*-nitrophenol to the NTP for toxicity and carcinogenicity studies. These studies were conducted by dermal application of *p*-nitrophenol in acetone to male and female Swiss-Webster mice. Swiss-Webster mice were selected because this mouse strain had been used in previous studies of *p*-nitrophenol conducted by the U.S. Army. The dermal route of administration was selected because of potential exposure of a large number of military personnel through treated footwear.

The selection of doses for the 18-month studies was based on information from an unpublished 13-week dermal study in Swiss-Webster mice. In that study, 10/10 males and 8/10 females in the 350 mg/kg dose group and 3/10 males and 1/10 females in the 175 mg/kg dose group died prior to study termination. Additionally, epidermal necrosis, hyperplasia, hyperkeratosis, and skin inflammation were observed primarily in the males receiving 175 and 350 mg/kg and in the females receiving 350 mg/kg. Therefore, the doses chosen for the 18-month studies were 40 mg/kg for the low dose, 80 mg/kg for the mid dose, and 160 mg/kg for the high dose. These doses were considered adequate for determining the potential dermal carcinogenicity of *p*-nitrophenol. There were no chemically related neoplastic or nonneoplastic effects associated with the dermal administration of *p*-nitrophenol to Swiss-Webster mice for 18-months. Any subtle nonneoplastic effects may have been obscured by the development of spontaneous, age-related, generalized amyloidosis. Since no lesions relative to compound administration were observed in this study, a higher dose could possibly have been tolerated; however, based on the results of the unpublished 13-week dermal study a doubled dose could not have been tolerated.

Relatively few mice died during the first 60 weeks of these studies, but thereafter survival decreased abruptly in all dosed and control groups. Less than 50% of the animals in all dose groups, including controls, were alive at 80 weeks. Histopathologic examination of these animals revealed the presence of amyloid deposition in several organs, with particularly severe lesions in the kidneys where significant glomerular destruction was evident. Since this condition was observed with the same incidence and severity among untreated sentinel animals as well as among treated animals, the amyloidosis was not attributed to either *p*-nitrophenol or the acetone vehicle. Although no specific information on the life span of Swiss-Webster mice could be found in the literature, the appearance of amyloidosis in these studies indicates that they were approaching the end of their natural life span.

Amyloidosis is a metabolic disease common in several strains of mice and hamsters. The kidney is the organ most frequently affected by amyloidosis. Amyloidosis in mice, as in hamsters, is strain-, sex-, and age-dependent. It is rare in mice less than 6 months old, but the incidence and severity increase significantly beyond 1 year of age. The appearance of amyloid is associated with aging in several strains of mice, including those derived from Swiss-Webster mice, such as Swiss-CFW and CD-1 mice. Some strains of mice have relatively low incidences of this disease, while others may have incidences approaching 100% in older animals (Heston and Deringer, 1948; West and Murphy, 1965; Dunn, 1967) including LLC (Chai, 1978), KK (Soret *et al.*, 1977), and SJL/J (Scheinberg *et al.*, 1976) mice.

The incidences of amyloidosis in various strains of mice, including the Swiss-Webster CD-1 strain, have been reviewed. Conner *et al.* (1983) found the incidence of amyloidosis in CD-1 mice was 100% in mice surviving beyond 14 months. In another review of amyloidosis, Burek *et al.* (1988) reported that the incidence of the disease in CD-1 mice surviving to

between 92 and 104 weeks of age was 57% for males and 52% for females. Rao *et al.* (1988) observed that survival of ICR Swiss CD-1 mice in control groups was 79% for males and 73% for females at 19 months, 45% and 62% at 22 months, and 46% and 45% after 24 months. In reviewing the literature, Rao *et al.* (1988) reported that the incidences of renal amyloidosis varied in 23- to 25-month-old CD-1 mice. In one study, amyloid incidence in the kidney was as great as 55% for males and 57% for females, while other studies reported amyloid incidences in the kidneys ranging from 13% to 33% in males and from 17% to 52% in females. The incidence of amyloidosis in $B6C3F_1$ mice is among the lowest, with less than 5% in the kidneys of 26-month-old mice.

The toxicity of *p*-nitrophenol has been partially characterized; the single oral LD_{50} is 620 mg/kg for Sprague-Dawley rats and 470 mg/kg for CF-1 mice. There is little information available on the effects of chronic exposure to *p*-nitrophenol. As benzyl derivatives, most phenols, especially di- and tri-hydroxy phenols, are readily absorbed through the skin, but less polar benzyl derivatives, such as benzene or toluene, are not absorbed as readily by the skin (Sittig, 1985). The toxic effects of phenols vary somewhat depending on the substituted groups present but the nitro group of *p*-nitrophenol is considered to be the most toxic. In animals, the most commonly observed toxic effects are on the central nervous system. Although the central nervous system is depressed, in general, by *p*-nitrophenol, central and peripheral vagus stimulation does occur (Clayton and Clayton, 1981). In these NTP studies, no clinical findings were observed relative to the central nervous system.

The NTP has evaluated the ability of four commonly used *in vitro* short-term genetic toxicity tests to predict rodent carcinogenicity. These tests include induction of mutations in *Salmonella typhimurium*, and induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). The *S. typhimurium* assay was shown to have the lowest sensitivity (0.48 = proportion of carcinogens positive in *S. typhimurium*), the highest specificity (0.91 = proportion of noncarcinogens negative in *S. typhimurium*), and the highest positive predictivity for carcinogenicity (89% of the chemicals mutagenic in *S. typhimurium* were carcinogenic in rodents) of these *in vitro* tests. The aromatic nitro group of *p*-nitrophenol represents a structural alert to DNA reactivity (Tennant and Ashby, 1991), and the *S. typhimurium* test is particularly sensitive to chemicals with this substructure. The fact that *p*-nitrophenol did not induce gene mutations in *S. typhimurium* and was negative in essentially all other short-term tests for genotoxicity confirms its designation as a nongenotoxic chemical. These negative genotoxicity results are predictive of the lack of carcinogenic activity observed in the bioassay (Tennant *et al.*, 1990).

CONCLUSIONS

Under the conditions of these 18-month dermal studies there was *no evidence of carcinogenic activity** in male or female Swiss-Webster mice receiving 40, 80, or 160 mg/kg *p*-nitrophenol.

*Explanation of Levels of Evidence of Carcinogenic Activity appears on page 8. A summary of Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

REFERENCES

Amacher, D.E., and Turner, G.N. (1982). Mutagenic evaluation of carcinogens and non-carcinogens in the L5178Y/TK assay utilizing postmitochondrial fractions (S9) from normal rat liver. *Mutat. Res.* 97, 49-65.

Angerhofer, R.A. (1985). Effect of dermal applications of paranitrophenol on the reproductive functions of rats. No. AD-A157120, p. 38. Army Environmental Hygiene Agency, U.S. Army, Aberdeen Proving Ground, MD.

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

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

Boutwell, R.K. and Bosch, D.K. (1959). The tumor-promoting action of phenol and related compounds for mouse skin. *Cancer Res.* 19, 413-424.

Burek, J.D., Duprat, P., Owen, R., Peter, C.P., and VanZwieten, M.J. (1988). Renal diseases in laboratory animals. In *International Review of Experimental Pathology*, pp. 231-319. Academic Press, Inc., San Diego, CA.

Buselmaier, W., Roehrborn, G., and Propping, P. (1972). Mutagenicity investigations with pesticides in the host-mediated assay and the dominant lethal test in mice. *Biol. Zentralbl.* 91, 311-325.

Chai, C.K. (1978). Spontaneous amyloidosis in LLC mice. *Am. J. Path.* 90, 381-398.

Clayton, G.D., and Clayton, F.E. (1981). *Patty's Industrial Hygiene and Toxicology: Volume 2A*, 3rd ed., p. 2473. John Wiley and Sons, New York.

Cliet, I., Fournier, E., Melcion, C., and Cordier, A. (1989). *In vivo* micronucleus tests in mouse. Comparison of the sensitivity of three target organs (bone marrow, liver, and testis) to six carcinogens. *Environ. Mol. Mutagen.* 14 (Suppl. 15), 39. (Abstr.)

Code of Federal Regulations (CFR), 21, part 58.

Commoner, B. (1976). Reliability of bacterial mutagenesis techniques to distinguish carcinogenic and noncarcinogenic chemicals. USNTISPB Report EPA-600/1-76-022.

Conner, M.W., Conner, B.H., Fox, J.G., and Rogers, A.E. (1983). Spontaneous amyloidosis in outbred CD-1 mice. *Surv. Synth. Path. Res.* 1, 67-78.

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

DeFlora, S., Zanacchi, P., Camoirano, A., Bennicelli, C., and Badolati, G.S. (1984a). Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. *Mutat. Res.* 133, 161-198.

DeFlora, S., Camoirano, A., Zanacchi, P., and Bennicelli, C. (1984b). Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other *Salmonella* strains. *Mutat. Res.* 134, 159-165.

Degawa, M., Shoji, Y., Masuko, K., and Hashimoto, Y. (1979). Mutagenicity of metabolites of carcinogenic aminoazo dyes. *Cancer Lett.* (Amsterdam) 8, 71-76.

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

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumor prevalence data. *J. R. Stat. Soc.* **C32**, 236-248.

Dunn, T.B. (1967). In *Pathology of Laboratory Rats and Mice* (E. Cotchin and F.J.C. Roe, Eds.). pp. 181-212. Blackwell, Oxford.

Eiche, A., Bexell, G., and Sandelin, K. (1990). Genotoxicity of *p*-aminophenol in somatic and germ line cells of *Drosophila melanogaster*. *Mutat. Res.* **240**, 87-92.

Galloway, S.M., Bloom, A.D., Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985). Development of a standard protocol for *in vitro* cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. *Environ. Mutagen.* **7**, 1-51.

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

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

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

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* **5** (Suppl. 1), 3-142.

Hayward, N.K., Lavin, M.F., and Craswell, P.W. (1982). Inhibition of DNA synthesis and alteration to DNA structure by the phenacetin analog *p*-aminophenol. *Biochem. Pharmacol.* **31**, 1425-1429.

Heston, W.E., and Deringer, M.K. (1948). Hereditary renal disease and amyloidosis in mice. *Arch. Path.* **46**, 49-58.

Ho, Y.L., and Ho., S.K. (1981). Screening of carcinogens with the prophage λcl*ts*857 induction test. *Cancer Res.* **41**, 532-536.

Hossack, D.J.N., and Richardson, J.C. (1977). Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. *Experientia* **33**, 377-378.

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

Kavaler, A.R. (1987). Chemical Profile; *p*-nitrophenol. *Chem. Mark. Rep.* **232** (13), 50.

Lavoie, E., Tulley, L., Fow, E., and Hoffmann, D. (1979). Mutagenicity of aminophenyl and nitrophenyl ethers, sulfides, and disulfides. *Mutat. Res.* **67**, 123-131.

Margolin, B., Collings, B., and Mason, J. (1983). Statistical analysis and sample size determinations for mutagenicity experiments with binomial responses. *Environ. Mutagen.* **5**, 705-710.

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

Matula, T.I., Vezina, M., and Downie, R. (1984). Mutagenicity of phenazopyridine and its urinary metabolites. *Environ. Mutagen.* **6**, 452. (Abstr.)

McCann, J., Choi, E., Yamasaki, E., and Ames, B.N. (1975). Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc. Natl. Acad. Sci. USA* **72**, 5135-5139.

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

The Merck Index (1983). 10th ed. (M. Windholz, Ed.), p. 950. Merck, Rahway, NJ.

Mitra, A.B., and Manna, G.K. (1971). Effect of some phenolic compounds on chromosomes of bone marrow cells of mice. *Indian J. Med. Res.* 59, 1442-1447.

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

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

National Institutes of Health (NIH) (1978). Open formula rat and mouse ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

Nojma, K., Kawaguchi, A., Ohya, T., Kanno, S., and Hirobe, M. (1983). Studies on photochemical reaction of air pollutants. X. Identification of nitrophenols in suspended particulates. *Chem. Pharm. Bull.* 31, 1047-1051.

Oberly, T.J., Bewsey, B.J., and Probst, G.S. (1984). An evaluation of the L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay using 42 chemicals. *Mutat. Res.* 125, 291-306.

Peña-Egido, M.J., Marino-Hernandez, E.L., Santos-Buelga, C., and Rivas-Gonzalo, J.C. (1988). Urinary excretion kinetics of *p*-nitrophenol following oral administration of parathion in the rabbit. *Arch. Toxicol.* 62, 351-354.

Probst, G.S., McMahon, R.E., Hill, L.E., Thompson, C.Z., Epp, J.K., and Neal, S.B. (1981). Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: comparison with bacterial mutagenicity using 218 compounds. *Environ. Mutagen.* 3, 11-32.

Rao, G.N., Birnbaum, L.S., Collins, J.J., Tennant, R.W., and Skow, L.C. (1988). Mouse strains for chemical carcinogenicity studies: Overview of a workshop. *Fundam. Appl. Toxicol.* 10, 385-394.

Rickert, D.E., Bond, J.A., Long, R.M., and Chism, J.P. (1983). Metabolism and excretion of nitrobenzene by rats and mice. *Toxicol. Appl. Pharmacol.* 67, 206-214.

Rumack, B.H., and Spoerke, D.G. (1991). *Poisindex®* Information System. Micromedex, Inc., Denver, CO.

Sadtler Standard Spectra. (1976). IR No. 5891, UV No. 1624, NMR No. 6814M. Sadtler Research Laboratories, Philadelphia, PA.

Scheinberg, M.A., Cathcart, E.S., Eastcott, J.W., Skinner, M., Benson, M., Shirahama, T., and Bennett, M. (1976). The SJL/J mouse: A new model for spontaneous age-associated amyloidosis. *Lab. Invest.* 35, 47-54.

Shimizu, M., and Yano, E. (1986). Mutagenicity of mono-nitrobenzene derivatives in the Ames test and rec assay. *Mutat. Res.* 170, 11-22.

Sittig, M. (1985). Nitrophenols. In *Handbook of Toxic and Hazardous Chemicals and Carcinogens*, 2nd Ed., p. 664. Noyes Data Corporation, Park Ridge, NJ.

Smith, L.W., Hall, G.T., and Kennedy, G.L. (1988). Acute and repeated dose inhalation toxicity of para-nitrophenol sodium salt in rats. *Drug. Chem. Toxicol.* 11 (3), 319-327.

Soret, M.G., Peterson, T., Wyse, B., Block, E.M., and Dulin, W.E. (1977). Renal amyloidosis in KK mice that may be misinterpreted as diabetic glomerulosclerosis. *Arch. Path. Lab. Med.* 101, 464-468.

Suzuki, J., Koyama, T., and Suzuki, S. (1983). Mutagenicities of mono-nitrobenzene derivatives in the presence of norharman. *Mutat. Res.* **120**, 105-110.

Takehisa, S., and Kanaya, N. (1982). SCE induction in human lymphocytes by combined treatment with aniline and norharman. *Mutat. Res.* **101**, 165-172.

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

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

Tennant, R.W., Spalding, J., Stasiewicz, S., and Ashby, J. (1990). Prediction of the outcome of rodent carcinogenicity bioassays currently being conducted on 44 chemicals by the National Toxicology Program. *Mutagenesis* **5**, 3-14.

Tennant, R.W., and Ashby, J. (1991). Classification according to chemical structure, mutagenicity to *Salmonella* and level of carcinogenicity of a further 39 chemicals tested for carcinogenicity by the U.S. National Toxicology Program. *Mutat. Res.* **257**, 209-227.

Thompson, C.Z., Hill, L.E., Epp, J.K., and Probst, G.S. (1983). The induction of bacterial mutation and hepatocyte unscheduled DNA synthesis by monosubstituted anilines. *Environ. Mutagen.* **5**, 803-811.

U.S. Environmental Protection Agency (USEPA) (1980). Ambient Water Quality Criteria Document: Nitrophenol, C-10-14. U.S. EPA, Washington, DC.

Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. (1977). Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. Appl. Pharmacol.* **42**, 417-423.

West, W.T., and Murphy, E.D. (1965). Sequence of deposition of amyloid in strain A mice and relationship to renal disease. *J. Natl. Cancer Inst.* **35**, 167-174.

Wild, D., Eckhardt, K., Gocke, E., and King, M.T. (1980). Comparative results of short-term *in vitro* and *in vivo* mutagenicity tests obtained with selected environmental chemicals. In *Short-term Tests Carcinog. Proc. Symp.* (K.H. Norpoth and R.C. Garner, Eds.) pp. 170-178. Springer-Verlag, Berlin.

Wild, D., King, M.T., Eckhardt, K., and Gocke, E. (1981). Mutagenic activity of aminophenols and diphenols, and relations with chemical structure. *Mutat. Res.* **85**, 456. (Abstr.)

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988). *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. Mol. Mutagen.* 11 (Suppl. 12), 1-157.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 114.

Zimmering, S., Mason, J.M., Valencia, R., and Woodruff, R.C. (1985). Chemical mutagenesis testing in *Drosophila*. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* **7**, 87-100.

APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 18-MONTH DERMAL STUDY OF *p*-NITROPHENOL

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accident	4	1		3
Moribund	22	34	23	21
Natural deaths	5	8	11	12
Survivors				
Died last week of study	1			1
Terminal sacrifice	28	17	26	23
Animals examined microscopically	56	59	60	57
Alimentary System				
Gallbladder	(47)	(46)	(50)	(45)
Intestine large, colon	(52)	(53)	(53)	(51)
Carcinoma			1 (2%)	
Intestine large, rectum	(51)	(51)	(51)	(50)
Cystadenoma		1 (2%)		
Intestine small, ileum	(53)	(54)	(53)	(52)
Intestine small, jejunum	(53)	(50)	(51)	(48)
Liver	(56)	(58)	(60)	(57)
Hemangiosarcoma			1 (2%)	1 (2%)
Hemangiosarcoma, multiple			1 (2%)	
Hepatocellular adenoma	1 (2%)	3 (5%)	5 (8%)	1 (2%)
Mesentery	(2)	(2)	(1)	
Hemangiosarcoma	1 (50%)			
Pancreas	(56)	(57)	(60)	(57)
Salivary glands	(56)	(57)	(60)	(57)
Carcinoma	1 (2%)			
Stomach	(56)	(58)	(60)	(57)
Stomach, forestomach	(55)	(57)	(60)	(57)
Papilloma squamous	1 (2%)			
Stomach, glandular	(55)	(57)	(59)	(57)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(56)	(57)	(60)	(57)
Capsule, adenoma	1 (2%)			
Adrenal gland, cortex	(56)	(57)	(60)	(56)
Adenoma	4 (7%)	6 (11%)	6 (10%)	5 (9%)
Adenoma, multiple				1 (2%)
Bilateral, adenoma		1 (2%)		
Adrenal gland, medulla	(56)	(57)	(60)	(56)
Pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(55)	(55)	(58)	(56)
Adenoma	1 (2%)			
Pituitary gland	(50)	(53)	(50)	(49)
Pars distalis, carcinoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
General Body System				
Tissue NOS	(2)	(2)	(3)	
Lipoma	1 (50%)		3 (100%)	
Sarcoma	1 (50%)	1 (50%)		
Genital System				
Epididymis	(56)	(57)	(60)	(56)
Leiomyoma		1 (2%)		
Prostate	(52)	(53)	(54)	(45)
Carcinoma			1 (2%)	
Testes	(55)	(57)	(59)	(56)
Embryonal carcinoma		1 (2%)		
Hematopoietic System				
Bone marrow	(56)	(57)	(59)	(56)
Lymph node	(56)	(58)	(60)	(57)
Mediastinal, carcinoma, metastatic			1 (2%)	
Lymph node, mandibular	(53)	(57)	(60)	(57)
Lymph node, mesenteric	(53)	(57)	(60)	(55)
Spleen	(56)	(57)	(60)	(57)
Thymus	(42)	(44)	(43)	(39)
Integumentary System				
Skin	(56)	(59)	(60)	(57)
Hemangiosarcoma				1 (2%)
Site of application-mass, keratoacanthoma		1 (2%)		
Site of application-mass, papilloma				1 (2%)
Tail, hemangiosarcoma			1 (2%)	
Skin, site of application-no mass	(56)	(59)	(60)	(57)
Musculoskeletal System				
Bone	(56)	(59)	(59)	(57)
Nervous System				
Brain	(56)	(58)	(60)	(57)
Carcinoma, metastatic				1 (2%)
Respiratory System				
Lung	(56)	(57)	(60)	(57)
Alveolar/bronchiolar adenoma	4 (7%)	9 (16%)	12 (20%)	4 (7%)
Alveolar/bronchiolar adenoma, multiple		2 (4%)		1 (2%)
Alveolar/bronchiolar carcinoma	5 (9%)	8 (14%)	6 (10%)	6 (11%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		1 (2%)
Nose	(56)	(57)	(60)	(57)

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol
(continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Special Senses System				
Eye	(3)	(2)	(1)	(3)
Harderian gland		(1)	(2)	
Adenoma		1 (100%)		
Urinary System				
Kidney	(56)	(59)	(60)	(57)
Urinary bladder	(54)	(54)	(57)	(56)
Carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(56)	(59)	(60)	(57)
Leukemia			1 (2%)	
Lymphoma malignant histiocytic		2 (3%)	2 (3%)	
Lymphoma malignant lymphocytic	2 (4%)		1 (2%)	1 (2%)
Lymphoma malignant mixed	1 (2%)	1 (2%)	3 (5%)	1 (2%)
Lymphoma malignant undifferentiated cell		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	20	33	33	20
Total primary neoplasms	24	40	45	28
Total animals with benign neoplasms	13	23	22	11
Total benign neoplasms	13	25	27	13
Total animals with malignant neoplasms	9	13	14	13
Total malignant neoplasms	11	15	18	15
Total animals with metastatic neoplasms			1	1
Total metastatic neoplasms			1	1

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control

Number of Days on Study	2 2 2	3 9 7	4 0 9	4 1 2	4 1 9	4 2 3	4 7 5	4 8 5	4 8 6	4 8 6	4 8 6	4 9 2	4 9 3	5 0 8	5 1 0	5 1 0	5 1 0	5 1 2	5 1 4	5 1 7	5 1 9	5 2 0	5 2 1	5 3 0	5 3 2
Carcass ID Number	0 4 6 1	0 2 1 1	0 3 3 1	0 1 7 1	0 2 4 1	0 3 1 1	0 4 9 1	0 0 6 1	0 2 0 1	0 2 2 1	0 2 6 1	0 5 8 1	0 1 6 1	0 3 9 1	0 0 4 1	0 4 1 1	0 5 9 1	0 3 0 1	0 4 4 1	0 5 1 1	0 2 7 1	0 3 6 1	0 1 3 1	0 0 8 1	0 3 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	A	M	+	M	+	+	A	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Hemangiosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									X
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel								+																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	M	M	+	+	M	M	+	M	M	M	M	+	M	M	M	M	I	+	M	M	M	+
Pituitary gland	+	M	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 3 6	5 4 9	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	0 1 0 1	0 0 2 1	0 0 3 1	0 0 5 1	0 1 4 1	0 1 8 1	0 1 9 1	0 1 5 1	0 2 8 1	0 2 9 1	0 3 2 1	0 3 5 1	0 4 3 1	0 4 5 1	0 4 7 1	0 4 8 1	0 5 4 1	0 5 7 1	0 6 0 1	0 6 9 1	0 7 1 1	0 7 2 1	0 7 5 1	0 7 6 1	0 7 7 1	0 8 0 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																	
Mesentery													+							+						
Hemangiosarcoma																				X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																										
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																		X		X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X		
Parathyroid gland	+	M	M	M	M	+	+	+	+	M	+	+	+	+	M	+	+	M	M	M	+	+	+	M	M	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 3 4 4 5 5 5 7 0 2 0 2 3 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + +	56
Gallbladder	+ + + + + +	47
Intestine large	+ + + + + +	56
Intestine large, cecum	+ + + + + +	52
Intestine large, colon	+ + + + + +	52
Intestine large, rectum	+ + + + + +	51
Intestine small	+ + + + + +	56
Intestine small, duodenum	+ + + + + +	54
Intestine small, ileum	+ + + + + +	53
Intestine small, jejunum	+ + + + + +	53
Liver	+ + + + + +	56
Hepatocellular adenoma		1
Mesentery		2
Hemangiosarcoma		1
Pancreas	+ + + + + +	56
Salivary glands	+ + + + + +	56
Carcinoma		1
Stomach	+ + + + + +	56
Stomach, forestomach	+ + + + + +	55
Papilloma squamous		1
Stomach, glandular	+ + + + + +	55
Cardiovascular System		
Blood vessel		1
Heart	+ + + + + +	56
Endocrine System		
Adrenal gland	+ + + + + +	56
Capsule, adenoma	X	1
Adrenal gland, cortex	+ + + + + +	56
Adenoma	X	4
Adrenal gland, medulla	+ + + + + +	56
Islets, pancreatic	+ + + + + +	55
Adenoma		1
Parathyroid gland	+ M M M M M	22
Pituitary gland	+ + M + + +	50
Thyroid gland	+ + + + + +	56

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control
(continued)

Number of Days on Study	2	3	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5
	2	9	0	1	1	2	7	8	8	8	8	9	9	0	1	1	1	1	1	1	1	2	2	3	3
	2	7	9	2	9	3	5	5	6	6	6	2	3	8	0	0	0	2	4	7	9	0	1	0	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	2	3	1	2	3	4	0	2	2	2	5	1	3	0	4	5	3	4	5	2	3	1	0	3
	6	1	3	7	4	1	9	6	0	2	6	8	6	9	4	1	9	0	4	1	7	6	3	8	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS																									
Lipoma																									
Sarcoma																									
Genital System																									
Coagulating gland					+																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																+		+							
Preputial gland																					+				
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	M	+	+	I	A	+	+	+	+	+	+	+	M	+	+	+	I	+	M	A	+
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	+	M	+	M	+	M	M	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 3 6	5 4 9	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	0 1 0 1	0 0 2 1	0 0 3 1	0 0 5 1	0 1 4 1	0 1 8 1	0 1 9 1	0 2 5 1	0 2 8 1	0 2 9 1	0 3 2 1	0 3 5 1	0 4 3 1	0 4 5 1	0 4 7 1	0 4 8 1	0 5 4 1	0 5 7 1	0 5 9 1	0 1 1 1	0 1 2 1	0 5 5 1	0 5 6 1	0 5 7 1	0 6 0 1
General Body System																									
Tissue NOS							+															+			
Lipoma																						X			
Sarcoma							X																		
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis						+																			
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 3 4 4 5 5 5 7 0 2 0 2 3 1 1 1 1 1 1	**Total Tissues/ Tumors**
General Body System		
Tissue NOS		2
Lipoma		1
Sarcoma		1
Genital System		
Coagulating gland		1
Epididymis	+ + + + + +	56
Penis		3
Preputial gland	+	2
Prostate	+ + M I M +	52
Seminal vesicle	+ + + + + +	56
Testes	+ + + + + +	55
Hematopoietic System		
Bone marrow	+ + + + + +	56
Lymph node	+ + + + + +	56
Lymph node, mandibular	+ + + + + +	53
Lymph node, mesenteric	+ + + + M +	53
Spleen	+ + + + + +	56
Thymus	+ + M + M M	42
Integumentary System		
Mammary gland	M M M M M M	7
Skin	+ + + + + +	56
Skin, control	+ + + + + +	56
Skin, site of application-no mass	+ + + + + +	56
Musculoskeletal System		
Bone	+ + + + + +	56
Nervous System		
Brain	+ + + + + +	56

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	2 2 2	3 9 7	4 0 9	4 1 2	4 1 9	4 2 3	4 7 5	4 8 5	4 8 6	4 8 6	4 8 6	4 9 2	4 9 3	4 0 8	5 1 0	5 1 0	5 1 0	5 1 2	5 1 4	5 1 7	5 1 9	5 2 0	5 2 1	5 3 0	5 3 2
Carcass ID Number	0 4 6 1	0 2 1 1	0 3 3 1	0 1 7 1	0 2 4 1	0 3 1 1	0 4 9 1	0 0 6 1	0 2 0 1	0 2 2 1	0 2 6 1	0 5 8 1	0 1 6 1	0 3 9 1	0 0 4 1	0 4 1 1	0 5 9 1	0 3 0 1	0 4 4 1	0 5 1 1	0 2 7 1	0 3 6 1	0 1 3 1	0 0 8 1	0 3 8 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																				X		
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye				+		+					+														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed																									

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	3	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	6	9	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	1	1	1	2	2	2	3	3	4	4	4	4	5	0	0	1	1	5	5	5	5	6
	0	2	3	5	4	8	9	5	8	9	2	5	3	5	7	8	4	7	9	1	2	5	6	7	0	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X	X													
Alveolar/bronchiolar carcinoma	X									X														X	X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear										+																
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																										
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic							X																			
Lymphoma malignant mixed							X																			

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 3 4 4 5 5 5 7 0 2 0 2 3 1 1 1 1 1 1	**Total Tissues/ Tumors**
Respiratory System		
Lung	+ + + + + +	56
Alveolar/bronchiolar adenoma		4
Alveolar/bronchiolar carcinoma	X	5
Nose	+ + + + + +	56
Trachea	+ + + + + +	53
Special Senses System		
Ear		1
Eye		3
Urinary System		
Kidney	+ + + + + +	56
Urethra	+ +	2
Urinary bladder	+ + + + + +	54
Systemic Lesions		
Multiple organs	+ + + + + +	56
Lymphoma malignant lymphocytic		2
Lymphoma malignant mixed		1

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg

Number of Days on Study	1 2 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 2 9 9 0 3 9 2 3 4 4 4 4 4 6 7 7 7 8 8 8 8 8 9 9 9 1 0 2 4 2 7 0 8 2 2 3 7 9 3 0 0 5 2 6 6 6 6 0 3 3
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 7 4 3 4 6 6 3 4 3 6 4 5 3 5 5 6 7 4 2 3 4 7 5 3 4 7 6 7 0 5 3 0 8 5 1 1 8 1 2 0 8 4 2 6 6 9 2 3 8 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ + + + + + A + + + + + + + + + + + + + M + + + M +
Gallbladder	+ A A A + A A M + + + + + M A + + + + + + + + + + +
Intestine large	+ + + + + A + + + + + + + + + + + + + + + + + + +
Intestine large, cecum	+ A + A + A A + + + + + + + A A + + + + + + + + +
Intestine large, colon	+ + + A + A A + + + + + + + A + + + + + + + + + +
Intestine large, rectum	+ A + A + A A + + + + + + + A M + + + + + + + + +
Cystadenoma	X
Intestine small	+ + + + + A + + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ A + + + A A + + + + + + M A + + + + + + + + + +
Intestine small, ileum	+ A + A + A A + + + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ A + A + A A + + + + A + + A + + + + + + M M + +
Liver	+ + + + + A + + + + + + + + + + + + + + + + + + +
Hepatocellular adenoma	
Mesentery	+ +
Pancreas	+ + + + + A A + + + + + + + + + + + + + + + + + +
Salivary glands	+ + + + + A A + + + + + + + + + + + + + + + + + +
Stomach	+ + + + + A + + + + + + + + + + + + + + + + + + +
Stomach, forestomach	+ + + + + A A + + + + + + + + + + + + + + + + + +
Stomach, glandular	+ + + + + A A + + + + + + + + + + + + + + + + + +
Cardiovascular System	
Blood vessel	
Heart	+ +
Endocrine System	
Adrenal gland	+ + + + + A A + + + + + + + + + + + + + + + + + +
Adrenal gland, cortex	+ + + + + A A + + + + + + + + + + + + + + + + + +
Adenoma	
Bilateral, adenoma	
Adrenal gland, medulla	+ + + + + A A + + + + + + + + + + + + + + + + + +
Islets, pancreatic	+ + + + + A A + + + + + + + + + M + + + + + + + M +
Parathyroid gland	M M M M M M M M M + + + + + + + M + M I + + M M +
Pituitary gland	+ I + + + M A + + + + + + + + + + + + M + M + + + +
Thyroid gland	+ M + M + A A + + + + + + + + + + + + + + + + + + +

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	459	503	503	508	512	514	514	522	526	528	528	542	545	545	547	549	552	552	552	552	552	552	552	552
Carcass ID Number	12811	13211	14711	14411	16211	15111	16911	16611	12411	15511	17811	17611	12511	18011	15911	12311	17111	17211	12911	13311	13411	15511	16411	17711
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X	X										
Mesentery																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel											+													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																X			X	X		
Bilateral, adenoma																								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	M	+	M	+	+	+	M	+	M	M	M	M	+	+	M	M	M	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 3 3 4 4 5 5 5 6 6	
Carcass ID Number	1 1 1 1 1 1 1 1 1 3 4 6 6 5 6 7 2 2 9 3 4 7 7 0 3 1 2 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + + + +	56
Gallbladder	+ + + + + + + + +	46
Intestine large	+ + + + + + + + +	58
Intestine large, cecum	+ + + + + + + + +	52
Intestine large, colon	+ + + + + + + + +	53
Intestine large, rectum	+ + + + M + + + +	51
Cystadenoma		1
Intestine small	+ + + + + + + + +	58
Intestine small, duodenum	+ + + + + + + + +	53
Intestine small, ileum	+ + + + + + + + +	54
Intestine small, jejunum	+ + + + + + + + +	50
Liver	+ + + + + + + + +	58
Hepatocellular adenoma	X	3
Mesentery		2
Pancreas	+ + + + + + + + +	57
Salivary glands	+ + + + + + + + +	57
Stomach	+ + + + + + + + +	58
Stomach, forestomach	+ + + + + + + + +	57
Stomach, glandular	+ + + + + + + + +	57
Cardiovascular System		
Blood vessel		1
Heart	+ + + + + + + + +	59
Endocrine System		
Adrenal gland	+ + + + + + + + +	57
Adrenal gland, cortex	+ + + + + + + + +	57
Adenoma	X X	6
Bilateral, adenoma	X	1
Adrenal gland, medulla	+ + + + + + + + +	57
Islets, pancreatic	+ + + + + + + + +	55
Parathyroid gland	M + + + M M M M M	24
Pituitary gland	+ + + + + + + + +	53
Thyroid gland	+ + + + + + + + +	55

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	1 2 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
	2 9 9 0 3 9 2 3 4 4 4 4 4 6 7 7 7 8 8 8 8 8 9 9 9
	1 0 2 4 2 7 0 8 2 2 3 7 9 3 0 0 5 2 6 6 6 6 0 3 3
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	7 4 3 4 6 6 3 4 3 6 4 5 3 5 5 6 7 4 2 3 4 7 5 3 4
	7 6 7 0 5 3 0 8 5 1 1 8 1 2 0 8 4 2 6 6 9 2 3 8 5
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
General Body System	
Tissue NOS	+ +
Sarcoma	X
Genital System	
Epididymis	+ + + + + A A + + + + + + + + + + + + + + + + + +
Leiomyoma	
Penis	
Preputial gland	A
Prostate	+ + + + + A A + + + + + + M + + + + + + + + M M +
Seminal vesicle	+ + + + + A A + + + + + + + + + + + + + + + + + +
Testes	+ + + + + A A + + + + + + + + + + + + + + + + + +
Embryonal carcinoma	X
Hematopoietic System	
Bone marrow	+ + + + + A A + + + + + + + + + + + + + + + + + +
Lymph node	+ + + + + A + + + + + + + + + + + + + + + + + + +
Lymph node, mandibular	+ + + + + A A + + + + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + A A + + + + + + + + + + + + + + + + + +
Spleen	+ + + + + A A + + + + + + + + + + + + + + + + + +
Thymus	+ + + + + A A + + + + + + + + + M + M + + + M + M +
Integumentary System	
Mammary gland	M M M M M A A M M M M M M M M M M M + M + + M M M +
Skin	+ +
Site of application-mass, keratoacanthoma	
Skin, control	+ +
Skin, site of application-no mass	+ +
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ + + + + A + + + + + + + + + + + + + + + + + + +

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	4 9 7	5 0 3	5 0 3	5 0 8	5 1 2	5 1 4	5 1 4	5 2 4	5 2 6	5 2 8	5 2 8	5 4 2	5 4 5	5 4 5	5 4 7	5 4 9	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2
Carcass ID Number	1 2 8 1	1 3 2 1	1 4 7 1	1 4 4 1	1 6 2 1	1 5 1 1	1 6 9 1	1 6 6 1	1 2 4 1	1 5 5 1	1 7 8 1	1 7 6 1	1 2 5 1	1 8 0 1	1 5 9 1	1 2 3 1	1 7 1 1	1 2 7 1	1 2 9 1	1 3 3 1	1 3 4 1	1 5 4 1	1 5 6 1	1 7 5 1	1 7 9 1
General Body System																									
Tissue NOS																									
Sarcoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																				X					
Penis										+															
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Embryonal carcinoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	I	I	+	M	+	M	+	+	+	+	I	+	+	+	+	M	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Site of application-mass, keratoacanthoma																									
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 3 3 4 4 5 5 5 6 6	
Carcass ID Number	1 1 1 1 1 1 1 1 1 3 4 6 6 5 6 7 2 2 9 3 4 7 7 0 3 1 2 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
General Body System		
Tissue NOS		2
Sarcoma		1
Genital System		
Epididymis	+ + + + + + + + +	57
Leiomyoma		1
Penis	+	2
Preputial gland		
Prostate	+ + + + + + + + +	53
Seminal vesicle	+ + + + + + + + +	56
Testes	+ + + + + + + + +	57
Embryonal carcinoma		1
Hematopoietic System		
Bone marrow	+ + + + + + + + +	57
Lymph node	+ + + + + + + + +	58
Lymph node, mandibular	+ + + + + + + + +	57
Lymph node, mesenteric	+ + + + + + + + +	57
Spleen	+ + + + + + + + +	57
Thymus	+ + + + + + I M +	44
Integumentary System		
Mammary gland	M + M M M M M M M	5
Skin	+ + + + + + + + +	59
Site of application-mass, keratoacanthoma	X	1
Skin, control	+ + + + + + + + +	59
Skin, site of application-no mass	+ + + + + + + + +	59
Musculoskeletal System		
Bone	+ + + + + + + + +	59
Nervous System		
Brain	+ + + + + + + + +	58

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	1 2 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 2 9 9 0 3 9 2 3 4 4 4 4 4 6 7 7 7 8 8 8 8 8 9 9 9 1 0 2 4 2 7 0 8 2 2 3 7 9 3 0 0 5 2 6 6 6 6 0 3 3
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 7 4 3 4 6 6 3 4 3 6 4 5 3 5 5 6 7 4 2 3 4 7 5 3 4 7 6 7 0 5 3 0 8 5 1 1 8 1 2 0 8 4 2 6 6 9 2 3 8 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Respiratory System	
Lung	+ + + + + A A + + + + + + + + + + + + + + + + + +
Alveolar/bronchiolar adenoma	X X X X X
Alveolar/bronchiolar adenoma, multiple	
Alveolar/bronchiolar carcinoma	X
Alveolar/bronchiolar carcinoma, multiple	
Nose	+ + + + + A A + + + + + + + + + + + + + + + + + +
Trachea	+ + + + + A A + + + + + + + + + + + + + + + + + +
Special Senses System	
Ear	+ +
Eye	+
Harderian gland	
Adenoma	
Urinary System	
Kidney	+ +
Urethra	+
Urinary bladder	+ A + + + A A + + + + + + + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant histiocytic	X
Lymphoma malignant mixed	
Lymphoma malignant undifferentiated cell type	

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	4 9 7	5 0 3	5 0 3	5 0 8	5 1 2	5 1 4	5 1 4	5 2 4	5 2 6	5 2 8	5 2 8	5 4 2	5 4 5	5 4 5	5 4 7	5 4 9	5 4 9	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2
Carcass ID Number	1 2 8 1	1 3 2 1	1 4 7 1	1 4 4 1	1 6 2 1	1 5 1 1	1 6 9 1	1 6 6 1	1 2 4 1	1 5 5 1	1 7 8 1	1 7 6 1	1 2 5 1	1 8 0 1	1 5 9 1	1 2 3 1	1 7 1 1	1 2 7 1	1 2 9 1	1 3 3 1	1 3 4 1	1 5 4 1	1 5 6 1	1 7 5 1	1 7 9 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X													X				X					X
Alveolar/bronchiolar adenoma, multiple													X												
Alveolar/bronchiolar carcinoma				X		X		X		X													X		
Alveolar/bronchiolar carcinoma, multiple																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									+
Eye					+		M																		
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic	X																								
Lymphoma malignant mixed	X																								
Lymphoma malignant undifferentiated cell type																			X						

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	
	5	5	5	5	5	5	5	5	5	
	3	3	4	4	5	5	5	6	6	
Carcass ID Number	1	1	1	1	1	1	1	1	1	**Total**
	3	4	6	6	5	6	7	2	2	**Tissues/**
	9	3	4	7	7	0	3	1	2	**Tumors**
	1	1	1	1	1	1	1	1	1	
Respiratory System										
Lung	+	+	+	+	+	+	+	+	+	57
Alveolar/bronchiolar adenoma										9
Alveolar/bronchiolar adenoma, multiple	X									2
Alveolar/bronchiolar carcinoma		X							X	8
Alveolar/bronchiolar carcinoma, multiple										1
Nose	+	+	+	+	+	+	+	+	+	57
Trachea	+	+	+	+	+	+	+	+	+	54
Special Senses System										
Ear										3
Eye										2
Harderian gland			+							1
Adenoma			X							1
Urinary System										
Kidney	+	+	+	+	+	+	+	+	+	59
Urethra										1
Urinary bladder	+	+	+	+	+	+	+	+	+	54
Systemic Lesions										
Multiple organs	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant histiocytic										2
Lymphoma malignant mixed										1
Lymphoma malignant undifferentiated cell type										1

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg

Number of Days on Study	1 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 2 9 2 6 8 2 2 3 3 4 5 5 5 5 6 7 9 0 1 1 1 1 1 1 1 3 5 2 3 1 3 5 7 2 0 2 4 8 4 5 3 0 0 0 0 2 2 4 7
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 7 6 7 9 6 4 7 8 4 6 6 8 9 9 9 4 4 8 4 5 5 4 5 7 7 8 5 9 1 0 3 6 1 7 9 3 9 4 6 7 5 4 5 6 6 8 9 4 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ +
Gallbladder	M A + A + + A A + + + + + + + + + + + + A + + + +
Intestine large	+ + + + + + A + + + + + + + + + + + + + + + + + +
Intestine large, cecum	+ + + A A + A A A + + A + + + + + + + A + + + + +
Intestine large, colon	+ + + + A + A A A + + A + + + + + + + + + + + + +
Carcinoma	X
Intestine large, rectum	M + M A + + A + A + + A + + + + + + + + A + + + + +
Intestine small	+ + + + + + A + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ M + A A + A + A + + A + + + + + + + + A M + + + +
Intestine small, ileum	+ + + + A + A A A + + + + + + + + + + + A + + + + +
Intestine small, jejunum	+ + + A A + A A A + + A + + + + + + + + A + + + + +
Liver	+ +
Hemangiosarcoma	
Hemangiosarcoma, multiple	
Hepatocellular adenoma	
Mesentery	+
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adenoma	X
Adrenal gland, medulla	+ +
Pheochromocytoma benign	
Islets, pancreatic	+ +
Parathyroid gland	+ M + M M + M M M + M M M + M M M + M + M M M M M
Pituitary gland	M + + + + + + + + + + M + + + + + + M + M M + M +
Thyroid gland	+ + + + + + + + + + + + M + M + + + M + + + + + +

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 1 8	5 1 9	5 2 0	5 3 1	5 3 3	5 3 6	5 4 5	5 4 7	5 5 0	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4
Carcass ID Number	2 6 1 1	2 5 3 1	2 5 2 1	2 5 1 1	2 4 8 1	2 8 8 1	2 6 7 1	2 7 0 1	2 9 8 1	2 5 5 1	2 5 7 1	2 5 9 1	2 6 2 1	2 6 4 1	2 9 0 1	2 9 2 1	2 9 3 1	2 4 1 1	2 4 2 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 9 5 1	2 9 9 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Intestine large, rectum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hemangiosarcoma, multiple																								X
Hepatocellular adenoma		X											X			X								
Mesentery																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel																								
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X					X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X				
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	M	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	M	+	M	M
Pituitary gland	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 5 5 6 6 6 6 6 6 6	
Carcass ID Number	3 2 2 2 2 2 2 2 2 2 0 6 6 5 8 8 8 8 8 8 0 6 8 0 0 2 3 4 6 7 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + + + + +	60
Gallbladder	+ + M + + M + + + +	50
Intestine large	+ + + + + + + + + +	59
Intestine large, cecum	+ + + + + + + + + +	50
Intestine large, colon	+ + + + + + + + + +	53
Carcinoma		1
Intestine large, rectum	+ + + + + + + + + +	51
Intestine small	+ + + + + + + + + +	59
Intestine small, duodenum	+ + + + + + + + + +	50
Intestine small, ileum	+ + + + + + + + + +	53
Intestine small, jejunum	+ + + + + + + + + +	51
Liver	+ + + + + + + + + +	60
Hemangiosarcoma	X	1
Hemangiosarcoma, multiple		1
Hepatocellular adenoma	X X	5
Mesentery		1
Pancreas	+ + + + + + + + + +	60
Salivary glands	+ + + + + + + + + +	60
Stomach	+ + + + + + + + + +	60
Stomach, forestomach	+ + + + + + + + + +	60
Stomach, glandular	+ + + + + + + + + +	59
Cardiovascular System		
Blood vessel		2
Heart	+ + + + + + + + + +	59
Endocrine System		
Adrenal gland	+ + + + + + + + + +	60
Adrenal gland, cortex	+ + + + + + + + + +	60
Adenoma	X X X	6
Adrenal gland, medulla	+ + + + + + + + + +	60
Pheochromocytoma benign		1
Islets, pancreatic	+ + + + + + + + + +	58
Parathyroid gland	+ + + + M + M M M M	26
Pituitary gland	+ + + + + + + + + +	50
Thyroid gland	+ + + + + + + + + +	57

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	1	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5
	2	9	2	6	8	2	2	3	3	4	5	5	5	5	6	7	9	0	1	1	1	1	1	1
	1	3	5	2	3	1	3	5	7	2	0	2	4	8	4	5	3	0	0	0	0	2	2	4	7
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	7	6	7	9	6	4	7	8	4	6	6	8	9	9	9	4	4	8	4	5	5	4	5	7	7
	8	5	9	1	0	3	6	1	7	9	3	9	4	6	7	5	4	5	6	6	8	9	4	7	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS																									
Lipoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Penis													M						+			+			
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, carcinoma, metastatic								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	A	I	M	+	M	+	+	+	M	+	+	I	+	M	M	M
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tail, hemangiosarcoma																									
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	1	2	3	3	3	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	8	9	0	1	3	6	5	7	0	2	2	2	2	2	2	2	2	3	3	3	3	3	3	4	4
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	5	5	5	4	8	6	7	9	5	5	5	6	6	9	9	9	4	4	7	7	7	7	9	9
	1	3	2	1	8	8	7	0	8	5	7	9	2	4	0	2	3	1	2	2	3	4	5	5	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS																				+					
Lipoma																				X					
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+										+						
Preputial gland														M											
Prostate	+	M	+	M	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	M	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tail, hemangiosarcoma																			X						
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 5 5 6 6 6 6 6 6 6	
Carcass ID Number	3 2 2 2 2 2 2 2 2 2 0 6 6 5 8 8 8 8 8 8 0 6 8 0 0 2 3 4 6 7 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
General Body System		
Tissue NOS	+ +	3
Lipoma	X X	3
Genital System		
Epididymis	+ + + + + + + + + +	60
Penis		4
Preputial gland		
Prostate	+ + + + + + + + + +	54
Carcinoma		1
Seminal vesicle	+ + + + + + + + + +	60
Testes	+ + + + + + + + + +	59
Hematopoietic System		
Bone marrow	+ + + + + + + + + +	59
Lymph node	+ + + + + + + + + +	60
Mediastinal, carcinoma, metastatic		1
Lymph node, mandibular	+ + + + + + + + + +	60
Lymph node, mesenteric	+ + + + + + + + + +	60
Spleen	+ + + + + + + + + +	60
Thymus	+ + + + M + + + + +	43
Integumentary System		
Mammary gland	M M M + M M M M M M	3
Skin	+ + + + + + + + + +	60
Tail, hemangiosarcoma		1
Skin, control	+ + + + + + + + + +	60
Skin, site of application-no mass	+ + + + + + + + + +	60
Musculoskeletal System		
Bone	+ + + + + + + + + +	59
Nervous System		
Brain	+ + + + + + + + + +	60

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	1 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 2 9 2 6 8 2 2 3 3 4 5 5 5 5 6 7 9 0 1 1 1 1 1 1 1 1 3 5 2 3 1 3 5 7 2 0 2 4 8 4 5 3 0 0 0 0 2 2 4 7
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 7 6 7 9 6 4 7 8 4 6 6 8 9 9 9 4 4 8 4 5 5 4 5 7 7 8 5 9 1 0 3 6 1 7 9 3 9 4 6 7 5 4 5 6 6 8 9 4 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X X
Alveolar/bronchiolar carcinoma	X X X X X
Nose	+ +
Trachea	+ + + + + + + + + + + + + + + M + + + + + + + + +
Special Senses System	
Ear	+ + +
Eye	
Harderian gland	+ +
Urinary System	
Kidney	+ +
Urethra	+
Urinary bladder	+ + + + + + + A A + + + + + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia	
Lymphoma malignant histiocytic	X
Lymphoma malignant lymphocytic	X
Lymphoma malignant mixed	X

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 1 8	5 1 9	5 2 0	5 3 1	5 3 3	5 3 6	5 4 5	5 4 7	5 5 0	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4
Carcass ID Number	2 6 1 1	2 5 3 1	2 5 2 1	2 5 1 1	2 4 8 1	2 8 8 1	2 6 7 1	2 7 0 1	2 9 8 1	2 5 5 1	2 5 7 1	2 5 9 1	2 6 2 1	2 6 4 1	2 9 0 1	2 9 2 1	2 9 3 1	2 4 1 1	2 4 2 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 9 5 1	2 9 9 1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X		X						X		X							X				X		
Alveolar/bronchiolar carcinoma					X														X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Eye											+															
Harderian gland																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra			+																					+		
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia							X																			
Lymphoma malignant histiocytic																			X							
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed												X											X			

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg (continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	
	5	5	5	5	5	5	5	5	5	5	
	4	5	5	6	6	6	6	6	6	6	
Carcass ID Number	3	2	2	2	2	2	2	2	2	2	Total
	0	6	6	5	8	8	8	8	8	8	Tissues/
	0	6	8	0	0	2	3	4	6	7	Tumors
	1	1	1	1	1	1	1	1	1	1	
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma					X				X		12
Alveolar/bronchiolar carcinoma											6
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	58
Special Senses System											
Ear									+		4
Eye											1
Harderian gland											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Urethra											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	57
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia											1
Lymphoma malignant histiocytic											2
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed											3

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg

Number of Days on Study	1 9 5	2 6 8	3 1 7	3 8 5	3 9 5	4 1 2	4 2 7	4 3 7	4 4 1	4 4 2	4 4 5	4 4 7	4 6 3	4 7 4	4 7 8	4 7 8	4 8 0	4 8 2	4 8 4	4 8 4	4 8 6	4 8 6	4 8 7	4 9 3	5 0 4
Carcass ID Number	3 7 6 1	4 0 3 1	4 0 9 1	3 8 2 1	3 9 1 1	4 0 7 1	3 9 4 1	3 9 6 1	4 1 6 1	3 7 5 1	3 8 5 1	4 0 8 1	3 6 2 1	3 9 0 1	3 6 8 1	3 8 9 1	4 0 1 1	3 8 8 1	3 6 6 1	3 9 2 1	3 9 7 1	4 1 9 1	3 6 1 1	3 6 9 1	4 0 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	A	A	A	A	+	M	A	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+
Intestine large	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	A	+	+	A	A	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+
Intestine large, rectum	+	+	+	+	A	A	+	+	A	A	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	A	A	+	+	A	A	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	A	A	+	+	A	A	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular adenoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel		+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Adenoma, multiple																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	+	M	+	+	+	M	M	+	M	+	+	M	+	+	+	M	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Pars distalis, carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 0 7	5 0 9	5 1 3	5 1 4	5 1 7	5 2 8	5 2 8	5 4 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 5	5 5 5	5 5 5
Carcass ID Number	4 1 5 1	4 0 0 1	3 8 1 1	4 2 0 1	4 1 3 1	3 8 3 1	4 0 4 1	3 6 7 1	4 1 0 1	4 1 2 1	4 1 4 1	3 6 3 1	3 6 4 1	3 6 5 1	3 7 0 1	3 7 1 1	3 7 2 1	3 7 9 1	3 9 3 1	3 9 5 1	4 1 7 1	4 1 8 1	3 7 4 1	3 8 6 1	3 8 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular adenoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X					X								X											
Adenoma, multiple																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	M	M	+	M	M	M	+	+	M	M	M	+	+	+	+	M	M	M	M	M	+
Pituitary gland	+	M	+	I	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 4 4 7 7 8 9 9 0 0 3 7 0 8 9 5 6 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + +	56
Gallbladder	+ + + + + + +	45
Intestine large	+ + + + + + +	56
Intestine large, cecum	+ + + + + + +	51
Intestine large, colon	+ + + + + + +	51
Intestine large, rectum	+ + + + + + +	50
Intestine small	+ + + + + + +	56
Intestine small, duodenum	+ + + + M + +	46
Intestine small, ileum	+ + + M + + +	52
Intestine small, jejunum	+ + + + + + +	48
Liver	+ + + + + + +	57
Hemangiosarcoma	X	1
Hepatocellular adenoma	X	1
Pancreas	+ + + + + + +	57
Salivary glands	+ + + + + + +	57
Stomach	+ + + + + + +	57
Stomach, forestomach	+ + + + + + +	57
Stomach, glandular	+ + + + + + +	57
Cardiovascular System		
Blood vessel		1
Heart	+ + + + + + +	57
Endocrine System		
Adrenal gland	+ + + + + + +	57
Adrenal gland, cortex	+ + + + + + +	56
Adenoma	X	5
Adenoma, multiple	X	1
Adrenal gland, medulla	+ + + + + + +	56
Islets, pancreatic	+ + + + + M +	56
Parathyroid gland	+ M M + M M +	28
Pituitary gland	+ + I + + + +	49
Pars distalis, carcinoma		1
Thyroid gland	+ + + + + + +	56
General Body System		
None		

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	1 9 5	2 6 8	3 1 7	3 8 5	3 9 5	4 1 2	4 2 7	4 3 7	4 4 1	4 4 2	4 4 5	4 4 7	4 6 3	4 7 4	4 7 8	4 7 8	4 8 0	4 8 2	4 8 4	4 8 4	4 8 6	4 8 6	4 8 7	4 9 3	5 0 4
Carcass ID Number	3 7 6 1	4 0 3 1	4 0 9 1	3 8 2 1	3 9 1 1	4 0 7 1	3 9 4 1	3 9 6 1	4 1 6 1	3 7 5 1	3 8 5 1	4 0 8 1	3 6 2 1	3 9 0 1	3 6 8 1	3 8 9 1	4 0 1 1	3 8 8 1	3 6 6 1	3 9 2 1	3 9 7 1	4 1 9 1	3 6 1 1	3 6 9 1	4 0 2 1
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Penis						+													+						
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	M	M	+	M
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	I	+	+	I	+	+	M	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	M	I
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Site of application-mass, papilloma																				X					
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic							X																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	0	0	1	1	1	2	2	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	7	9	3	4	7	8	8	2	2	2	2	3	3	3	3	3	3	3	3	3	4	4	5	5	5
Carcass ID Number	4	4	3	4	4	3	4	3	4	4	4	3	3	3	3	3	3	3	3	4	4	3	3	3	
	1	0	8	2	1	8	0	6	1	1	1	6	6	6	7	7	7	7	9	9	1	1	7	8	8
	5	0	1	0	3	3	4	7	0	2	4	3	4	5	0	1	2	9	3	5	7	8	4	6	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland																									
Prostate	+	+	+	I	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	M	+	M	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	M	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Site of application-mass, papilloma																									
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X			X										
Alveolar/bronchiolar adenoma, multiple																									X
Alveolar/bronchiolar carcinoma				X					X	X	X														
Alveolar/bronchiolar carcinoma, multiple															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 4 4 7 7 8 9 9 0 0 3 7 0 8 9 5 6 1 1 1 1 1 1 1	Total Tissues/ Tumors
Genital System		
Coagulating gland	+	1
Epididymis	+ + + + + + +	56
Penis		2
Preputial gland	+	1
Prostate	+ M M + M + +	45
Seminal vesicle	+ + + + + + +	57
Testes	+ + + + + + +	56
Hematopoietic System		
Bone marrow	+ + + + + + +	56
Lymph node	+ + + + + + +	57
Lymph node, mandibular	+ + + + + + +	57
Lymph node, mesenteric	+ + + + + + +	55
Spleen	+ + + + + + +	57
Thymus	+ + M + + + +	39
Integumentary System		
Mammary gland	M M M + M M M	4
Skin	+ + + + + + +	57
Hemangiosarcoma		1
Site of application-mass, papilloma		1
Skin, control	+ + + + + + +	57
Skin, site of application-no mass	+ + + + + + +	57
Musculoskeletal System		
Bone	+ + + + + + +	57
Nervous System		
Brain	+ + + + + + +	57
Carcinoma, metastatic		1
Respiratory System		
Lung	+ + + + + + +	57
Alveolar/bronchiolar adenoma		4
Alveolar/bronchiolar adenoma, multiple		1
Alveolar/bronchiolar carcinoma	X X	6
Alveolar/bronchiolar carcinoma, multiple		1
Nose	+ + + + + + +	57
Trachea	+ + + + + + +	56

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	1 9 5	2 6 8	3 1 7	3 8 5	3 9 5	4 1 2	4 2 7	4 3 7	4 4 1	4 4 2	4 4 5	4 4 7	4 6 3	4 7 4	4 7 8	4 7 8	4 8 0	4 8 2	4 8 4	4 8 4	4 8 6	4 8 6	4 8 7	4 9 3	5 0 4
Carcass ID Number	3 7 6 1	4 0 3 1	4 0 9 1	3 8 2 1	3 9 1 1	4 0 7 1	3 9 4 1	3 9 6 1	4 1 6 1	3 7 5 1	3 8 5 1	4 0 8 1	3 6 2 1	3 9 0 1	3 6 8 1	3 8 9 1	4 0 1 1	3 8 8 1	3 6 6 1	3 9 2 1	3 9 7 1	4 1 9 1	3 6 1 1	3 6 9 1	4 0 2 1
Special Senses System																									
Ear																								+	
Eye								+											+		+				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																							+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Carcinoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed								X																	

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 4 4 7 7 8 9 9 0 0 3 7 0 8 9 5 6 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Special Senses System		
Ear		4
Eye		3
Urinary System		
Kidney	+ + + + + + +	57
Urethra	+	2
Urinary bladder	+ + + + + + +	56
Carcinoma		1
Systemic Lesions		
Multiple organs	+ + + + + + +	57
Lymphoma malignant lymphocytic		1
Lymphoma malignant mixed		1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Adrenal Gland (Cortex): Adenoma				
Overall rates[a]	4/60 (7%)	7/58 (12%)	6/60 (10%)	6/59 (10%)
Adjusted rates[b]	13.2%	37.3%	20.1%	20.5%
Terminal rates[c]	3/29 (10%)	6/17 (35%)	4/26 (15%)	3/23 (13%)
First incidence (days)	536	503	435	442
Life table tests[d]	P=0.328	P=0.060	P=0.322	P=0.250
Logistic regression tests[d]	P=0.301	P=0.115	P=0.348	P=0.272
Cochran-Armitage test[d]	P=0.393			
Fisher exact test[d]		P=0.245	P=0.372	P=0.361
Liver: Hepatocellular Adenoma				
Overall rates	1/60 (2%)	3/59 (5%)	5/60 (8%)	1/60 (2%)
Adjusted rates	3.4%	14.7%	17.9%	4.2%
Terminal rates	1/29 (3%)	1/17 (6%)	4/26 (15%)	1/24 (4%)
First incidence (days)	552 (T)	545	519	552 (T)
Life table tests	P=0.583N	P=0.167	P=0.082	P=0.720
Logistic regression tests	P=0.569	P=0.192	P=0.092	P=0.720
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.303	P=0.103	P=0.752N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	4/60 (7%)	11/58 (19%)	12/60 (20%)	6/60 (10%)
Adjusted rates	11.2%	35.8%	34.0%	20.2%
Terminal rates	2/29 (7%)	3/17 (18%)	6/26 (23%)	4/24 (17%)
First incidence (days)	409	438	454	442
Life table tests	P=0.409	P=0.014	P=0.024	P=0.282
Logistic regression tests	P=0.467	P=0.034	P=0.028	P=0.341
Cochran-Armitage test	P=0.498			
Fisher exact test		P=0.041	P=0.029	P=0.372
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	5/60 (8%)	9/58 (16%)	6/60 (10%)	7/60 (12%)
Adjusted rates	16.6%	35.6%	14.6%	27.6%
Terminal rates	4/29 (14%)	4/17 (24%)	1/26 (4%)	6/24 (25%)
First incidence (days)	536	486	293	514
Life table tests	P=0.387	P=0.047	P=0.469	P=0.247
Logistic regression tests	P=0.417	P=0.099	P=0.499	P=0.231
Cochran-Armitage test	P=0.468			
Fisher exact test		P=0.179	P=0.500	P=0.381
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	9/60 (15%)	20/58 (34%)	17/60 (28%)	11/60 (18%)
Adjusted rates	26.8%	61.4%	42.4%	38.3%
Terminal rates	6/29 (21%)	7/17 (41%)	7/26 (27%)	8/24 (33%)
First incidence (days)	409	438	293	442
Life table tests	P=0.494	P=0.001	P=0.051	P=0.248
Logistic regression tests	P=0.505N	P=0.005	P=0.058	P=0.287
Cochran-Armitage test	P=0.455N			
Fisher exact test		P=0.012	P=0.060	P=0.404

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol
(continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Tissue NOS: Lipoma				
Overall rates	1/60 (2%)	0/60 (0%)	3/60 (5%)	0/60 (0%)
Adjusted rates	3.4%	0.0%	11.5%	0.0%
Terminal rates	1/29 (3%)	0/17 (0%)	3/26 (12%)	0/24 (0%)
First incidence (days)	552 (T)	–[e]	552 (T)	–
Life table tests	P=0.517N	P=0.607N	P=0.265	P=0.538N
Logistic regression tests	P=0.517N	P=0.607N	P=0.265	P=0.538N
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.500N	P=0.309	P=0.500N
All Organs: Hemangiosarcoma				
Overall rates	1/60 (2%)	0/60 (0%)	3/60 (5%)	2/60 (3%)
Adjusted rates	3.4%	0.0%	11.5%	6.6%
Terminal rates	1/29 (3%)	0/17 (0%)	3/26 (12%)	1/24 (4%)
First incidence (days)	552 (T)	–	552 (T)	482
Life table tests	P=0.225	P=0.607N	P=0.265	P=0.433
Logistic regression tests	P=0.206	P=0.607N	P=0.265	P=0.461
Cochran-Armitage test	P=0.242			
Fisher exact test		P=0.500N	P=0.309	P=0.500
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	2/60 (3%)	3/60 (5%)	5/60 (8%)	2/60 (3%)
Adjusted rates	5.3%	10.4%	15.3%	5.1%
Terminal rates	1/29 (3%)	1/17 (6%)	3/26 (12%)	0/24 (0%)
First incidence (days)	423	442	362	437
Life table tests	P=0.543	P=0.389	P=0.200	P=0.651
Logistic regression tests	P=0.579N	P=0.501	P=0.219	P=0.686N
Cochran-Armitage test	P=0.579			
Fisher exact test		P=0.500	P=0.219	P=0.691N
All Organs: Benign Neoplasms				
Overall rates	13/60 (22%)	23/60 (38%)	22/60 (37%)	12/60 (20%)
Adjusted rates	38.4%	76.6%	60.6%	38.3%
Terminal rates	9/29 (31%)	11/17 (65%)	13/26 (50%)	7/24 (29%)
First incidence (days)	409	438	435	442
Life table tests	P=0.386N	P<0.001	P=0.033	P=0.474
Logistic regression tests	P=0.355N	P=0.007	P=0.040	P=0.548
Cochran-Armitage test	P=0.266N			
Fisher exact test		P=0.036	P=0.054	P=0.500N
All Organs: Malignant Neoplasms				
Overall rates	9/60 (15%)	13/60 (22%)	14/60 (23%)	13/60 (22%)
Adjusted rates	28.0%	44.6%	36.9%	41.6%
Terminal rates	7/29 (24%)	5/17 (29%)	6/26 (23%)	8/24 (33%)
First incidence (days)	423	442	293	427
Life table tests	P=0.190	P=0.051	P=0.148	P=0.124
Logistic regression tests	P=0.218	P=0.156	P=0.172	P=0.159
Cochran-Armitage test	P=0.249			
Fisher exact test		P=0.240	P=0.177	P=0.240

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
All Organs: Benign and Malignant Neoplasms				
Overall rates	20/60 (33%)	33/60 (55%)	33/60 (55%)	21/60 (35%)
Adjusted rates	57.7%	87.7%	79.1%	58.7%
Terminal rates	15/29 (52%)	13/17 (76%)	18/26 (69%)	11/24 (46%)
First incidence (days)	409	438	293	427
Life table tests	P=0.503	P<0.001	P=0.008	P=0.250
Logistic regression tests	P=0.479N	P=0.002	P=0.009	P=0.350
Cochran-Armitage test	P=0.388N			
Fisher exact test		P=0.013	P=0.013	P=0.500

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accident	4	1		3
Moribund	22	34	23	21
Natural deaths	5	8	11	12
Survivors				
Died last week of study	1			1
Terminal sacrifice	28	17	26	23
Animals examined microscopically	56	59	60	57
Alimentary System				
Esophagus	(56)	(56)	(60)	(56)
Amyloid deposition	1 (2%)	1 (2%)		1 (2%)
Gallbladder	(47)	(46)	(50)	(45)
Hyperplasia, lymphoid				1 (2%)
Inflammation, chronic	2 (4%)		1 (2%)	
Intestine large, cecum	(52)	(52)	(50)	(51)
Amyloid deposition		2 (4%)		1 (2%)
Edema		1 (2%)		1 (2%)
Intestine large, colon	(52)	(53)	(53)	(51)
Amyloid deposition		1 (2%)		1 (2%)
Edema	1 (2%)	7 (13%)	4 (8%)	1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Polyarteritis			1 (2%)	2 (4%)
Intestine large, rectum	(51)	(51)	(51)	(50)
Amyloid deposition		2 (4%)		1 (2%)
Intestine small	(56)	(58)	(59)	(56)
Mucosa, abscess	1 (2%)			
Intestine small, duodenum	(54)	(53)	(50)	(46)
Amyloid deposition	27 (50%)	19 (36%)	12 (24%)	12 (26%)
Intussusception		1 (2%)		
Intestine small, ileum	(53)	(54)	(53)	(52)
Amyloid deposition	36 (68%)	40 (74%)	36 (68%)	37 (71%)
Edema			1 (2%)	1 (2%)
Hemorrhage				1 (2%)
Necrosis				1 (2%)
Intestine small, jejunum	(53)	(50)	(51)	(48)
Amyloid deposition	29 (55%)	32 (64%)	28 (55%)	21 (44%)
Liver	(56)	(58)	(60)	(57)
Amyloid deposition	33 (59%)	41 (71%)	31 (52%)	33 (58%)
Degeneration, fatty	1 (2%)			
Granuloma			1 (2%)	
Hematopoietic cell proliferation		2 (3%)	2 (3%)	2 (4%)
Inflammation, chronic, focal	17 (30%)	12 (21%)	17 (28%)	16 (28%)
Mitotic alteration	1 (2%)		1 (2%)	
Necrosis			1 (2%)	
Necrosis, focal	2 (4%)	1 (2%)	1 (2%)	4 (7%)
Pigmentation		1 (2%)		
Bile duct, hyperplasia			1 (2%)	
Centrilobular, hypertrophy	2 (4%)	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Alimentary System (continued)				
Mesentery	(2)	(2)	(1)	
Granuloma	1 (50%)			
Polyarteritis		1 (50%)	1 (100%)	
Fat, necrosis, focal		1 (50%)		
Pancreas	(56)	(57)	(60)	(57)
Amyloid deposition, focal		1 (2%)		
Focal cellular change	2 (4%)	1 (2%)	2 (3%)	
Inflammation, suppurative, focal			1 (2%)	
Polyarteritis			1 (2%)	1 (2%)
Acinus, amyloid deposition	1 (2%)	1 (2%)	3 (5%)	1 (2%)
Acinus, hyperplasia, focal		1 (2%)		
Acinus, hypertrophy, focal	1 (2%)	2 (4%)		
Duct, cyst			1 (2%)	
Interlobular, edema	16 (29%)	23 (40%)	11 (18%)	14 (25%)
Salivary glands	(56)	(57)	(60)	(57)
Amyloid deposition	27 (48%)	39 (68%)	33 (55%)	28 (49%)
Infarct	1 (2%)			
Inflammation, chronic	1 (2%)			
Inflammation, suppurative, focal			1 (2%)	1 (2%)
Interlobular, edema	11 (20%)	14 (25%)	9 (15%)	9 (16%)
Stomach	(56)	(58)	(60)	(57)
Pylorus, amyloid deposition		1 (2%)		
Submucosa, edema		2 (3%)		1 (2%)
Stomach, forestomach	(55)	(57)	(60)	(57)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis				1 (2%)
Inflammation, chronic	1 (2%)			
Stomach, glandular	(55)	(57)	(59)	(57)
Acanthosis	1 (2%)			
Amyloid deposition	1 (2%)	5 (9%)	4 (7%)	1 (2%)
Submucosa, inflammation, acute		1 (2%)		
Cardiovascular System				
Blood vessel	(1)	(1)	(2)	(1)
Polyarteritis		1 (100%)	1 (50%)	
Aorta, inflammation, chronic			1 (50%)	1 (100%)
Aorta, thrombus	1 (100%)			
Heart	(56)	(59)	(59)	(57)
Amyloid deposition	35 (63%)	41 (69%)	34 (58%)	32 (56%)
Fibrosis			1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic, focal	1 (2%)			
Necrosis, focal			2 (3%)	1 (2%)
Polyarteritis			2 (3%)	1 (2%)
Atrium, thrombus	10 (18%)	16 (27%)	9 (15%)	4 (7%)
Pericardium, inflammation, subacute, focal			1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Endocrine System				
Adrenal gland	(56)	(57)	(60)	(57)
Capsule, hyperplasia	42 (75%)	37 (65%)	40 (67%)	36 (63%)
Corticomedullary junction, amyloid deposition	36 (64%)	39 (68%)	32 (53%)	30 (53%)
Corticomedullary junction, mineralization, focal				1 (2%)
Corticomedullary junction, pigmentation	32 (57%)	28 (49%)	35 (58%)	33 (58%)
Extra adrenal tissue, hemorrhage			1 (2%)	
Adrenal gland, cortex	(56)	(57)	(60)	(56)
Atrophy				1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, focal	3 (5%)		1 (2%)	
Hypertrophy, focal		1 (2%)	2 (3%)	1 (2%)
Hypoplasia		2 (4%)	1 (2%)	
Necrosis	1 (2%)			1 (2%)
Parathyroid gland	(22)	(24)	(26)	(28)
Amyloid deposition	12 (55%)	13 (54%)	6 (23%)	8 (29%)
Pituitary gland	(50)	(53)	(50)	(49)
Pars distalis, cyst	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Pars distalis, hyperplasia, focal	1 (2%)			
Thyroid gland	(56)	(55)	(57)	(56)
Amyloid deposition	32 (57%)	30 (55%)	24 (42%)	19 (34%)
Inflammation, chronic		2 (4%)	1 (2%)	1 (2%)
C-cell, hyperplasia	1 (2%)		1 (2%)	2 (4%)
Follicle, dilatation	10 (18%)	7 (13%)	11 (19%)	9 (16%)
Follicular cell, hyperplasia		2 (4%)	1 (2%)	1 (2%)
General Body System				
Tissue NOS	(2)	(2)	(3)	
Hemorrhage		1 (50%)		
Genital System				
Coagulating gland	(1)			(1)
Dilatation	1 (100%)			1 (100%)
Epididymis	(56)	(57)	(60)	(56)
Edema		1 (2%)	1 (2%)	
Granuloma sperm			1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	3 (5%)	2 (3%)	1 (2%)
Necrosis	1 (2%)			
Fat, inflammation, suppurative, focal		1 (2%)		
Fat, necrosis	1 (2%)			
Penis	(3)	(2)	(4)	(2)
Inflammation, acute				1 (50%)
Preputial gland	(2)			(1)
Abscess	1 (50%)			1 (100%)
Cyst	1 (50%)			
Prostate	(52)	(53)	(54)	(45)
Hyperplasia, focal		2 (4%)		
Inflammation, chronic	2 (4%)	3 (6%)	1 (2%)	
Inflammation, suppurative				3 (7%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Genital System (continued)				
Seminal vesicle	(56)	(56)	(60)	(57)
Abscess				1 (2%)
Concretion	1 (2%)	1 (2%)		
Dilatation	6 (11%)	6 (11%)	3 (5%)	4 (7%)
Hemorrhage	1 (2%)			
Inflammation, chronic	1 (2%)	5 (9%)		1 (2%)
Testes	(55)	(57)	(59)	(56)
Cyst			1 (2%)	
Granuloma sperm		1 (2%)	1 (2%)	
Interstitial cell, hyperplasia	1 (2%)			
Seminiferous tubule, atrophy	3 (5%)	8 (14%)	7 (12%)	9 (16%)
Seminiferous tubule, degeneration	3 (5%)	1 (2%)	3 (5%)	1 (2%)
Seminiferous tubule, mineralization	1 (2%)	2 (4%)		1 (2%)
Seminiferous tubule, necrosis	1 (2%)			
Tunic, inflammation, suppurative				1 (2%)
Hematopoietic System				
Bone marrow	(56)	(57)	(59)	(56)
Calvarium, myelofibrosis	1 (2%)			
Lymph node	(56)	(58)	(60)	(57)
Mediastinal, hyperplasia				1 (2%)
Mediastinal, hyperplasia, plasma cell				1 (2%)
Lymph node, mandibular	(53)	(57)	(60)	(57)
Amyloid deposition	1 (2%)			1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia, plasma cell	2 (4%)	2 (4%)	2 (3%)	
Lymph node, mesenteric	(53)	(57)	(60)	(55)
Abscess			1 (2%)	1 (2%)
Amyloid deposition	4 (8%)	5 (9%)	6 (10%)	6 (11%)
Granuloma		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage			2 (3%)	
Hyperplasia			1 (2%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, plasma cell				1 (2%)
Polyarteritis	1 (2%)			
Spleen	(56)	(57)	(60)	(57)
Amyloid deposition	30 (54%)	33 (58%)	23 (38%)	27 (47%)
Hematopoietic cell proliferation	42 (75%)	48 (84%)	48 (80%)	47 (82%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Pigmentation, hemosiderin	7 (13%)	9 (16%)	9 (15%)	11 (19%)
Thymus	(42)	(44)	(43)	(39)
Abscess		1 (2%)		
Amyloid deposition	1 (2%)			
Cyst				1 (3%)
Depletion lymphoid			1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Integumentary System				
Skin	(56)	(59)	(60)	(57)
Acanthosis				1 (2%)
Edema	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Exudate, focal		1 (2%)		
Abdominal, edema	1 (2%)			
Abdominal, inflammation, chronic				1 (2%)
Abdominal, dermis, inflammation, chronic		1 (2%)		
Abdominal, subcutaneous tissue, edema	17 (30%)	24 (41%)	16 (27%)	18 (32%)
Face, acanthosis		1 (2%)		
Face, exudate		1 (2%)		
Face, ulcer				1 (2%)
Foot, ulcer			1 (2%)	
Head, ulcer				1 (2%)
Head, ventral, ulcer		1 (2%)		
Neck, acanthosis		1 (2%)		
Neck, fungus		1 (2%)		
Neck, inflammation, subacute		1 (2%)		
Neck, ulcer	1 (2%)	2 (3%)		
Neck, subcutaneous tissue, hemorrhage			1 (2%)	
Other, inflammation, chronic				2 (4%)
Other, ulcer				2 (4%)
Right, forelimb, ulcer		1 (2%)		
Subcutaneous tissue, inflammation, chronic		1 (2%)		
Subcutaneous tissue, other, abscess				1 (2%)
Tail, inflammation, chronic			1 (2%)	
Skin, control	(56)	(59)	(60)	(57)
Dermis, inflammation, chronic	2 (4%)	1 (2%)		3 (5%)
Subcutaneous tissue, edema	7 (13%)	17 (29%)	9 (15%)	6 (11%)
Subcutaneous tissue, hemorrhage		1 (2%)		
Skin, site of application-no mass	(56)	(59)	(60)	(57)
Acanthosis	1 (2%)	3 (5%)	3 (5%)	1 (2%)
Exudate			2 (3%)	
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Ulcer		1 (2%)	3 (5%)	
Dermis, inflammation, chronic		5 (8%)	4 (7%)	3 (5%)
Subcutaneous tissue, edema	6 (11%)	8 (14%)	5 (8%)	1 (2%)
Musculoskeletal System				
Bone	(56)	(59)	(59)	(57)
Sternum, hyperostosis			1 (2%)	
Nervous System				
Brain	(56)	(58)	(60)	(57)
Hydrocephalus				1 (2%)
Perivascular, infiltration cellular, lymphocyte		1 (2%)		
Thalamus, mineralization, focal	18 (32%)	11 (19%)	16 (27%)	12 (21%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Respiratory System				
Lung	(56)	(57)	(60)	(57)
Amyloid deposition, focal		2 (4%)		
Congestion	2 (4%)	5 (9%)	4 (7%)	8 (14%)
Foreign body	1 (2%)			
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	3 (5%)
Inflammation, chronic, focal	13 (23%)	9 (16%)	13 (22%)	7 (12%)
Inflammation, subacute, focal				1 (2%)
Alveolar epithelium, hyperplasia, focal	5 (9%)	1 (2%)	2 (3%)	2 (4%)
Alveolus, infiltration cellular, histiocyte, focal	6 (11%)	5 (9%)	6 (10%)	6 (11%)
Artery, amyloid deposition	4 (7%)	1 (2%)	1 (2%)	
Interstitium, inflammation, chronic	4 (7%)	15 (26%)	6 (10%)	11 (19%)
Nose	(56)	(57)	(60)	(57)
Exudate	1 (2%)			
Foreign body	3 (5%)	2 (4%)	1 (2%)	1 (2%)
Fungus	1 (2%)		1 (2%)	
Inflammation, suppurative		1 (2%)		1 (2%)
Nasolacrimal duct, hemorrhage			1 (2%)	
Nasolacrimal duct, hyperplasia			1 (2%)	
Septum, amyloid deposition			1 (2%)	1 (2%)
Sinus, inflammation, chronic			1 (2%)	
Special Senses System				
Ear	(1)	(3)	(4)	(4)
Ulcer	1 (100%)	1 (33%)	2 (50%)	3 (75%)
Bilateral, ulcer		2 (67%)	1 (25%)	
External ear, acanthosis		1 (33%)		
Pinna, inflammation, chronic				1 (25%)
Eye	(3)	(2)	(1)	(3)
Cataract	1 (33%)			1 (33%)
Lids, inflammation, chronic				1 (33%)
Urinary System				
Kidney	(56)	(59)	(60)	(57)
Amyloid deposition	42 (75%)	44 (75%)	41 (68%)	38 (67%)
Atrophy, diffuse				1 (2%)
Hemorrhage			1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)	
Infarct				1 (2%)
Inflammation, chronic, focal				1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)	2 (4%)
Nephropathy	6 (11%)	4 (7%)	6 (10%)	5 (9%)
Cortex, atrophy, focal	4 (7%)	3 (5%)	2 (3%)	
Cortex, cyst	6 (11%)	9 (15%)	7 (12%)	7 (12%)
Cortex, renal tubule, mineralization, focal	4 (7%)	2 (3%)	1 (2%)	1 (2%)
Pelvis, dilatation	2 (4%)	4 (7%)	4 (7%)	2 (4%)
Perirenal tissue, hemorrhage			1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Urinary System (continued)				
Urethra	(2)	(1)	(3)	(2)
Bulbourethral gland, dilatation	2 (100%)	1 (100%)	2 (67%)	2 (100%)
Urinary bladder	(54)	(54)	(57)	(56)
Amyloid deposition	2 (4%)	1 (2%)	3 (5%)	2 (4%)
Crystals		1 (2%)		1 (2%)
Hemorrhage			1 (2%)	
Inflammation, suppurative				2 (4%)
Mucosa, hyperplasia		2 (4%)	1 (2%)	2 (4%)

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 18-MONTH DERMAL STUDY OF *p*-NITROPHENOL

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accident				1
Moribund	20	27	22	25
Natural deaths	5	7	5	7
Survivors				
Terminal sacrifice	35	26	33	27
Animals examined microscopically	60	60	60	59
Alimentary System				
Gallbladder	(53)	(53)	(56)	(53)
Adenocarcinoma		1 (2%)		
Intestine large, cecum	(57)	(56)	(59)	(55)
Intestine large, colon	(56)	(56)	(58)	(56)
Adenocarcinoma	1 (2%)			
Intestine small, duodenum	(58)	(56)	(57)	(52)
Adenocarcinoma			1 (2%)	
Polyp adenomatous	1 (2%)			
Intestine small, ileum	(57)	(57)	(60)	(55)
Polyp adenomatous	1 (2%)	1 (2%)		
Intestine small, jejunum	(55)	(54)	(56)	(54)
Hemangiosarcoma				1 (2%)
Liver	(60)	(60)	(60)	(59)
Hemangiosarcoma				1 (2%)
Sarcoma, metastatic				1 (2%)
Mesentery	(1)		(2)	(1)
Pancreas	(60)	(57)	(60)	(59)
Salivary glands	(60)	(59)	(60)	(59)
Stomach, forestomach	(60)	(60)	(60)	(59)
Papilloma squamous				2 (3%)
Stomach, glandular	(60)	(59)	(60)	(59)
Fibrous histiocytoma	1 (2%)			
Sarcoma				1 (2%)
Cardiovascular System				
Heart	(60)	(60)	(60)	(59)
Endocrine System				
Adrenal gland, cortex	(60)	(59)	(60)	(59)
Adrenal gland, medulla	(59)	(58)	(59)	(59)
Pheochromocytoma benign			1 (2%)	
Parathyroid gland	(34)	(30)	(30)	(24)
Pituitary gland	(54)	(56)	(54)	(55)
Pars distalis, adenoma	1 (2%)			
Thyroid gland	(58)	(58)	(56)	(58)
Follicular cell, adenoma	1 (2%)			1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
General Body System				
Tissue NOS		(1)	(1)	(1)
Fibrosarcoma			1 (100%)	
Sarcoma		1 (100%)		
Genital System				
Ovary	(60)	(57)	(60)	(58)
Adenoma			1 (2%)	1 (2%)
Granulosa cell tumor benign	1 (2%)			
Granulosa-theca tumor benign		1 (2%)		
Hemangiosarcoma		1 (2%)	1 (2%)	
Teratoma NOS	1 (2%)			
Thecoma benign	1 (2%)			
Thecoma malignant			1 (2%)	
Uterus	(60)	(58)	(60)	(58)
Adenocarcinoma	1 (2%)			
Hemangiosarcoma			1 (2%)	
Leiomyoma				1 (2%)
Leiomyosarcoma			1 (2%)	1 (2%)
Polyp stromal	4 (7%)	2 (3%)	6 (10%)	1 (2%)
Sarcoma stromal	1 (2%)	2 (3%)	1 (2%)	3 (5%)
Schwannoma malignant				2 (3%)
Cervix, fibroma				1 (2%)
Hematopoietic System				
Bone marrow	(59)	(60)	(58)	(59)
Lymph node	(60)	(60)	(60)	(59)
Lymph node, mandibular	(57)	(60)	(60)	(59)
Lymph node, mesenteric	(60)	(57)	(59)	(57)
Spleen	(60)	(60)	(60)	(59)
Hemangiosarcoma			1 (2%)	1 (2%)
Thymus	(47)	(49)	(42)	(46)
Integumentary System				
Mammary gland	(38)	(43)	(44)	(41)
Adenocarcinoma				1 (2%)
Skin	(60)	(60)	(60)	(59)
Other, trichoepithelioma			1 (2%)	
Skin, site of application-no mass	(60)	(60)	(60)	(59)
Musculoskeletal System				
None				
Nervous System				
Brain	(60)	(60)	(60)	(59)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol
(continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Respiratory System				
Lung	(60)	(60)	(60)	(59)
Alveolar/bronchiolar adenoma	7 (12%)	7 (12%)	8 (13%)	6 (10%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma	4 (7%)		2 (3%)	5 (8%)
Alveolar/bronchiolar carcinoma, multiple			2 (3%)	
Carcinoma		1 (2%)	1 (2%)	
Nose	(60)	(59)	(60)	(59)
Special Senses System				
Ear	(2)			
Fibrosarcoma	1 (50%)			
Harderian gland		(1)		(2)
Adenoma		1 (100%)		2 (100%)
Urinary System				
Kidney	(60)	(60)	(60)	(59)
Urinary bladder	(57)	(54)	(56)	(56)
Systemic Lesions				
Multiple organs[b]	(60)	(60)	(60)	(59)
Leukemia lymphocytic	1 (2%)	1 (2%)		
Lymphoma malignant histiocytic	2 (3%)	1 (2%)	2 (3%)	1 (2%)
Lymphoma malignant lymphocytic	2 (3%)		1 (2%)	
Lymphoma malignant mixed		1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant undifferentiated cell			2 (3%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	25	16	28	26
Total primary neoplasms	32	22	36	34
Total animals with benign neoplasms	15	10	15	14
Total benign neoplasms	17	13	17	16
Total animals with malignant neoplasms	13	8	16	17
Total malignant neoplasms	14	9	19	18
Total animals with metastatic neoplasms				1
Total metastatic neoplasms				1
Total animals with neoplasms uncertain-benign or malignant	1			
Total uncertain neoplasms	1			

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control

Number of Days on Study	1 2 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 2 9 7 7 3 4 4 4 5 6 7 7 7 8 8 9 9 9 0 1 1 1 1 2 2 0 5 0 3 8 2 7 8 0 3 2 5 5 3 5 3 3 7 5 0 1 2 2 0 8
Carcass ID Number	0 0 0 1 0 0 1 0 1 0 0 0 0 0 0 1 1 0 1 0 0 1 1 1 0 7 9 6 0 9 7 0 7 0 8 6 7 8 9 6 1 1 6 1 8 7 1 2 0 7 7 0 5 0 8 4 4 6 6 6 2 5 7 7 8 1 7 6 4 1 2 2 0 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ + + + + + + + + + + + + + + + + M + + + + + +
Gallbladder	M + M A + + + + + + + + + + + A + + A + M + + + + +
Intestine large	+ +
Intestine large, cecum	+ + + + + + + A + + + + + + + A + + A + + + + + +
Intestine large, colon	+ + + + + + A + + + + + + + A + + A + + + + + +
Adenocarcinoma	
Intestine large, rectum	+ + + + + + + + + + + + + + + + + A + + + + + +
Intestine small	+ +
Intestine small, duodenum	+ + + + + + + + + + + + + + + A + + + + + M + + +
Polyp adenomatous	X
Intestine small, ileum	+ + + + + + A + + + + + + + A + + + + + + + + + +
Polyp adenomatous	
Intestine small, jejunum	+ M + + + A + + + + + + + + A + + + + + + + + + M
Liver	+ +
Mesentery	+
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Fibrous histiocytoma	X
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	+ +
Islets, pancreatic	+ +
Parathyroid gland	+ M + M + + + M M + + + A M + M + + + M + M M M M
Pituitary gland	M + M + M
Pars distalis, adenoma	
Thyroid gland	+ M + +
Follicular cell, adenoma	X
General Body System	
None	

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control
(continued)

Number of Days on Study	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	0 6 7 1	0 6 9 1	0 7 0 1	0 7 9 1	0 8 0 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	0 8 8 1	0 8 9 1	0 9 9 1	0 9 9 1	1 1 5 1	1 1 6 1	1 1 8 1	1 1 9 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 5 1	0 9 6 1	1 0 3 1	1 0 5 1	1 0 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																		X							
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous														X											
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	I	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 6 6 6	
Carcass ID Number	1 1 1 1 0 0 0 0 0 0 0 1 1 7 7 6 6 6 8 9 0 3 3 8 1 3 4 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + + + +	58
Gallbladder	+ + + + + + + + +	52
Intestine large	+ + + + + + + + +	59
Intestine large, cecum	+ + + + + + + + +	56
Intestine large, colon	+ + + + + + + + +	55
Adenocarcinoma		1
Intestine large, rectum	+ + + + + + + + +	56
Intestine small	+ + + + + + + + +	59
Intestine small, duodenum	+ + + + + + + + +	57
Polyp adenomatous		1
Intestine small, ileum	+ + + + + + + + +	56
Polyp adenomatous		1
Intestine small, jejunum	+ + + + + + + + +	54
Liver	+ + + + + + + + +	59
Mesentery		1
Pancreas	+ + + + + + + + +	59
Salivary glands	+ + + + + + + + +	59
Stomach	+ + + + + + + + +	59
Stomach, forestomach	+ + + + + + + + +	59
Stomach, glandular	+ + + + + + + + +	59
Fibrous histiocytoma		1
Cardiovascular System		
Heart	+ + + + + + + + +	59
Endocrine System		
Adrenal gland	+ + + + + + + + +	59
Adrenal gland, cortex	+ + + + + + + + +	59
Adrenal gland, medulla	+ + + + + + + + +	58
Islets, pancreatic	+ + + + + + + + +	58
Parathyroid gland	M + M + + + + M +	34
Pituitary gland	+ + + + + + + + +	53
Pars distalis, adenoma		1
Thyroid gland	+ + M + + + + + +	57
Follicular cell, adenoma		1
General Body System		
None		

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control
(continued)

Number of Days on Study	1 2 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 2 9 7 7 3 4 4 4 5 6 7 7 7 8 8 9 9 9 0 1 1 1 1 2 2 0 5 0 3 8 2 7 8 0 3 2 5 5 3 5 3 3 7 5 0 1 2 2 0 8
Carcass ID Number	0 0 0 1 0 0 1 0 1 0 0 0 0 0 0 0 1 1 0 1 0 0 1 1 1 0 7 9 6 0 9 7 0 7 0 8 6 7 8 9 6 1 1 6 1 8 7 1 2 0 7 7 0 5 0 8 4 4 6 6 6 2 5 7 7 8 1 7 6 4 1 2 2 0 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Genital System	
Ovary	+ +
Granulosa cell tumor benign	
Teratoma NOS	X
Thecoma benign	X
Uterus	+ +
Adenocarcinoma	
Polyp stromal	X
Sarcoma stromal	X
Hematopoietic System	
Bone marrow	M +
Lymph node	+ +
Lymph node, mandibular	+ + + + + + + + + M + + M + + + + + + + + M + + +
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	+ + + + + M + + + + + + + + I + + + + M M M M I M
Integumentary System	
Mammary gland	+ + + M M M M M + + + + M M M M + M M M + + M M +
Skin	+ +
Skin, control	+ +
Skin, site of application-no mass	+ +
Musculoskeletal System	
Bone	M +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Alveolar/bronchiolar carcinoma	
Nose	+ +
Trachea	+ +

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	0 6 7 1	0 6 9 1	0 7 0 1	0 7 9 1	0 8 0 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	0 8 8 1	0 8 9 1	0 9 9 1	1 1 5 1	1 1 6 1	1 1 8 1	1 1 9 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 5 1	0 9 6 1	1 0 3 1	1 0 5 1	1 0 7 1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign			X																						
Teratoma NOS																									
Thecoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X
Polyp stromal												X								X	X				
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X						X					X							X
Alveolar/bronchiolar carcinoma				X						X					X		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 6 6 6	
Carcass ID Number	1 1 1 1 0 0 0 0 0 0 0 1 1 7 7 6 6 6 8 9 0 3 3 8 1 3 4 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Genital System		
Ovary	+ + + + + + + + +	59
Granulosa cell tumor benign		1
Teratoma NOS		1
Thecoma benign		1
Uterus	+ + + + + + + + +	59
Adenocarcinoma		1
Polyp stromal		4
Sarcoma stromal		1
Hematopoietic System		
Bone marrow	+ + + + + + + + +	58
Lymph node	+ + + + + + + + +	59
Lymph node, mandibular	+ + + + + + + + +	56
Lymph node, mesenteric	+ + + + + + + + +	59
Spleen	+ + + + + + + + +	59
Thymus	+ M + + + + + + +	46
Integumentary System		
Mammary gland	+ + M + + + + + +	38
Skin	+ + + + + + + + +	59
Skin, control	+ + + + + + + + +	59
Skin, site of application-no mass	+ + + + + + + + +	59
Musculoskeletal System		
Bone	+ + + + + + + + +	58
Nervous System		
Brain	+ + + + + + + + +	59
Respiratory System		
Lung	+ + + + + + + + +	59
Alveolar/bronchiolar adenoma		7
Alveolar/bronchiolar carcinoma		4
Nose	+ + + + + + + + +	59
Trachea	+ + + + + + + + +	59

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1	1	1
	6	6	7	7	8	8	8	8	8	8	8	9	1	1	1	1	1	9	9	9	9	9	9	0	0	0
	7	9	0	9	0	2	3	4	5	8	9	9	5	6	8	9	1	2	3	4	5	6	3	5	5	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System																										
Ear																								+		
Fibrosarcoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia lymphocytic																										
Lymphoma malignant histiocytic								X																		
Lymphoma malignant lymphocytic																										

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: Vehicle Control (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 6 6 6	
Carcass ID Number	1 1 1 1 0 0 0 0 0 0 0 1 1 7 7 6 6 6 8 9 0 3 3 8 1 3 4 1 1 1 1 1 1 1 1 1	Total Tissues/ Tumors
Special Senses System		
Ear		2
Fibrosarcoma		1
Urinary System		
Kidney	+ + + + + + + + +	59
Urinary bladder	+ + + + + + + + +	56
Systemic Lesions		
Multiple organs	+ + + + + + + + +	59
Leukemia lymphocytic		1
Lymphoma malignant histiocytic		2
Lymphoma malignant lymphocytic	X	2

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg

Number of Days on Study	2 2 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 5 6 6 6 6 7 4 4 4 5 5 5 7 7 7 8 8 8 9 9 9 9 9 9 9 0 3 6 1 7 5 0 2 9 0 0 6 3 7 8 2 2 6 2 7 7 7 7 7 8 0
Carcass ID Number	2 2 2 1 2 2 2 1 2 2 1 2 1 2 1 2 2 1 1 1 2 2 2 2 2 2 3 0 8 0 2 0 8 0 3 8 1 8 1 9 3 2 8 8 9 0 3 3 1 3 5 5 5 9 9 7 4 7 7 9 3 9 5 0 0 2 2 8 2 5 1 0 4 7 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ M
Gallbladder	A + + A A A + + + + M + + + + + + + + + + + M + A
Adenocarcinoma	X
Intestine large	+ + + + A A + + + + + + + + + + + + + + + + + + +
Intestine large, cecum	A + + + A A + + + + + + + + + + + + + + + + A + +
Intestine large, colon	A + + + A A + + + + M + + + + + + + + + + + + + +
Intestine large, rectum	A + + + A A + + + + + + M + + + + + + + + + + + +
Intestine small	+ + + + A A + + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	A + + + A A + + + + M + + + + + + + + + + + + + +
Intestine small, ileum	A + + + A A + + + + + + + + + + + + + + + + + + +
Polyp adenomatous	
Intestine small, jejunum	A + + + A A + + + M + + + + + + + + A + + + M + +
Liver	+ +
Pancreas	+ + + + A A + + + + + + + + + + + A + + + + + + +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ + + + + A + + + + + + + + + + + + + + + + + + +
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ + + + + A + + + + + + + + + + + + + + + + + + +
Adrenal gland, cortex	+ + + + + A + + + + + + + + + + + + + + + + + + +
Adrenal gland, medulla	+ + + + + A + + + + + + + + + + + + + + + + + + +
Islets, pancreatic	+ + + + A A + + + + + + + + + + + A + + + + + + +
Parathyroid gland	+ + + + + M M I + M + A + + M + + + M M + M + M M
Pituitary gland	+ M
Thyroid gland	+ M M
General Body System	
Tissue NOS	
Sarcoma	

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg (continued)

Number of Days on Study	5 0 0	5 0 4	5 1 7	5 2 9	5 3 0	5 3 2	5 4 2	5 4 5	5 4 9	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	2 3 7 1	2 1 4 1	1 9 9 1	2 2 6 1	1 9 3 1	2 1 3 1	2 3 6 1	2 1 2 1	2 1 5 1	1 8 1 1	1 8 4 1	1 8 6 1	1 9 1 1	1 9 2 1	2 1 1 1	2 1 6 1	2 1 8 1	2 2 0 1	2 2 1 1	1 9 4 1	1 9 6 1	1 9 7 1	1 9 8 1	2 0 0 1	2 0 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																							X		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	M	M	M	M	M	M	+	+	M	M	M	+	+	+	+	+	+	M	M	M
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS								+																	
Sarcoma								X																	

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 0 2 2 2 0 0 2 3 3 4 3 3 4 8 6 8 9 1 8 0 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + + + + +	59
Gallbladder	+ + + + + + + + + +	53
Adenocarcinoma		1
Intestine large	+ + + + + + + + + +	58
Intestine large, cecum	+ + + + + + + + + +	56
Intestine large, colon	+ + + + + + + + + +	56
Intestine large, rectum	+ + + + + + + + + +	55
Intestine small	+ + + + + + + + + +	58
Intestine small, duodenum	+ + + + + + + + + +	56
Intestine small, ileum	+ + + + + + + + + +	57
Polyp adenomatous		1
Intestine small, jejunum	+ + + + + + + + + +	54
Liver	+ + + + + + + + + +	60
Pancreas	+ + + + + + + + + +	57
Salivary glands	+ + + + + + + + + +	59
Stomach	+ + + + + + + + + +	60
Stomach, forestomach	+ + + + + + + + + +	60
Stomach, glandular	+ + + + + + + + + +	59
Cardiovascular System		
Heart	+ + + + + + + + + +	60
Endocrine System		
Adrenal gland	+ + + + + + + + + +	59
Adrenal gland, cortex	+ + + + + + + + + +	59
Adrenal gland, medulla	+ + + + + + + + + +	58
Islets, pancreatic	+ + + + + + + + + +	56
Parathyroid gland	+ M M M M + M + + +	30
Pituitary gland	+ + + + + + + + + +	56
Thyroid gland	+ + + + + + + + + +	58
General Body System		
Tissue NOS		1
Sarcoma		1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	2 6 3	2 6 6	3 6 1	3 6 7	3 7 5	4 4 0	4 4 2	4 4 9	4 5 0	4 5 0	4 5 0	4 7 6	4 7 3	4 7 7	4 7 8	4 8 2	4 8 2	4 8 6	4 9 2	4 9 7	4 9 7	4 9 7	4 9 7	4 9 7	4 9 8	4 9 1	5 0 0
Carcass ID Number	2 2 5 1	2 3 5 1	2 0 5 1	1 8 9 1	2 0 9 1	2 2 7 1	2 0 4 1	1 8 7 1	2 0 7 1	2 3 9 1	1 8 3 1	2 1 9 1	1 8 5 1	2 1 0 1	1 9 0 1	2 3 0 1	2 2 2 1	1 2 8 1	1 8 2 1	1 8 5 1	2 9 1 1	2 0 0 1	2 3 4 1	2 3 4 1	2 1 7 1	2 3 3 1
Genital System																											
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	
Granulosa-theca tumor benign								X																			
Hemangiosarcoma									X																		
Uterus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	
Polyp stromal																											
Sarcoma stromal															X												
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M		
Integumentary System																											
Mammary gland	+	+	M	+	M	M	+	M	M	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma								X	X																		
Alveolar/bronchiolar adenoma, multiple																											
Carcinoma																					X						
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I	M		

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 0 0	5 1 4	5 2 7	5 2 9	5 3 0	5 3 2	5 4 2	5 4 5	5 4 9	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 3	5 5 3	5 5 3	5 5 3	5 5 3	5 5 4	5 5 4	5 5 4	5 5 4	5 5 4
Carcass ID Number	2 3 7 1	2 1 4 1	1 9 9 1	2 2 6 1	1 9 3 1	2 1 3 1	2 3 6 1	2 1 2 1	2 1 5 1	1 8 1 1	1 8 4 1	1 8 6 1	1 9 1 1	1 9 2 1	1 1 1 1	2 1 6 1	2 1 8 1	2 2 0 1	2 2 1 1	1 9 4 1	1 9 6 1	1 9 7 1	1 9 8 1	2 0 0 1	2 0 2 1
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																								
Hemangiosarcoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X									X														
Sarcoma stromal																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	I	+	+	+	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	M	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X				X				X							X								
Alveolar/bronchiolar adenoma, multiple							X																	
Carcinoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 0 2 2 2 0 0 2 3 3 4 3 3 4 8 6 8 9 1 8 0 1 1 1 1 1 1 1 1 1 1	Total Tissues/ Tumors
Genital System		
Ovary	+ + + + + + + + + +	57
Granulosa-theca tumor benign		1
Hemangiosarcoma		1
Uterus	+ + + + + + + + + +	58
Polyp stromal		2
Sarcoma stromal	X	2
Hematopoietic System		
Bone marrow	+ + + + + + + + + +	60
Lymph node	+ + + + + + + + + +	60
Lymph node, mandibular	+ + + + + + + + + +	60
Lymph node, mesenteric	+ + + + + + + + + +	57
Spleen	+ + + + + + + + + +	60
Thymus	+ + + + + + + + + +	49
Integumentary System		
Mammary gland	+ + + + M + + + + +	43
Skin	+ + + + + + + + + +	60
Skin, control	+ + + + + + + + + +	60
Skin, site of application-no mass	+ + + + + + + + + +	60
Musculoskeletal System		
Bone	+ + + + + + + + + +	60
Nervous System		
Brain	+ + + + + + + + + +	60
Respiratory System		
Lung	+ + + + + + + + + +	60
Alveolar/bronchiolar adenoma	X	7
Alveolar/bronchiolar adenoma, multiple		1
Carcinoma		1
Nose	+ + + + + + + + + +	59
Trachea	+ + + + + + M + + +	55

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 40 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 0 2 2 2 0 0 2 3 3 4 3 3 4 8 6 8 9 1 8 0 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Special Senses System		
Harderian gland		1
Adenoma		1
Urinary System		
Kidney	+ + + + + + + + + +	60
Urethra	+	1
Urinary bladder	+ + + + + M M + + +	54
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	60
Leukemia lymphocytic		1
Lymphoma malignant histiocytic		1
Lymphoma malignant mixed		1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenl: 80 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	5	8	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	4	4	4	4	4	5	5
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	5	3	1	2	2	2	2	3	3	3	3	3	3	1	1	1	4	4	0	0	0	1	1	5	5
	2	9	9	3	6	7	8	0	1	4	5	7	8	5	7	8	3	5	7	8	9	0	2	5	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+																	+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	M	+	M	+	M	M	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Fibrosarcoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 5 5 5 6 0 0 0 0 4 5 7 8 9 0 2 3 4 6 9 4 1 1 1 1 1 1 1 1 1 1	Total Tissues/ Tumors
Alimentary System		
Esophagus	+ + + + + + + + + +	59
Gallbladder	+ + + + + + + + + +	56
Intestine large	+ + + + + + + + + +	60
Intestine large, cecum	+ + + + + + + + + +	59
Intestine large, colon	+ + + + + + + + + +	58
Intestine large, rectum	+ + M + + + + + + +	54
Intestine small	+ + + + + + + + + +	60
Intestine small, duodenum	+ + + + + + + + + +	57
Adenocarcinoma		1
Intestine small, ileum	+ + + + + + + + + +	60
Intestine small, jejunum	+ + + + + + + + + +	56
Liver	+ + + + + + + + + +	60
Mesentery		2
Pancreas	+ + + + + + + + + +	60
Salivary glands	+ + + + + + + + + +	60
Stomach	+ + + + + + + + + +	60
Stomach, forestomach	+ + + + + + + + + +	60
Stomach, glandular	+ + + + + + + + + +	60
Cardiovascular System		
Heart	+ + + + + + + + + +	60
Endocrine System		
Adrenal gland	+ + + + + + + + + +	60
Adrenal gland, cortex	+ + + + + + + + + +	60
Adrenal gland, medulla	+ + + + + + + + + +	59
Pheochromocytoma benign		1
Islets, pancreatic	+ + + + + + + + + +	56
Parathyroid gland	+ + M M + M M M + M	30
Pituitary gland	M + + + + + + + + +	54
Thyroid gland	+ + M + + + + + + +	56
General Body System		
Tissue NOS		1
Fibrosarcoma		1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 4 0 2 4 4 4 5 5 6 6 7 7 7 9 0 0 0 0 1 1 2 3 3 3 4 9 1 7 2 2 6 8 8 3 4 0 5 7 3 3 4 7 7 0 0 1 2 2 8 5
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 5 3 4 2 1 1 1 4 3 2 4 1 2 3 2 4 0 5 0 2 4 2 5 1 7 3 3 0 2 1 3 6 8 2 4 2 4 5 6 0 6 5 1 1 9 4 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Genital System	
Ovary	+ +
Adenoma	
Hemangiosarcoma	
Thecoma malignant	X
Uterus	+ +
Hemangiosarcoma	
Leiomyosarcoma	
Polyp stromal	X X X X
Sarcoma stromal	
Hematopoietic System	
Bone marrow	+ + + + + + + + + + + + + + + + + M + + + + + + A +
Lymph node	+ +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ + + + + + + A + + + + + + + + + + + + + + + + +
Spleen	+ +
Hemangiosarcoma	
Thymus	+ + M + + I + + + I + + + I + + M + M + + M + + M M +
Integumentary System	
Mammary gland	+ + + + M + M + + + + M + + + + + M M M M M M M M +
Skin	+ +
Other, trichoepithelioma	
Skin, control	+ +
Skin, site of application-no mass	+ +
Musculoskeletal System	
Bone	+ + + + + + + + + + + + + + + + + M + + + + + + + +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Alveolar/bronchiolar carcinoma	X X
Alveolar/bronchiolar carcinoma, multiple	X
Carcinoma	
Nose	+ +
Trachea	+ M +

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	545	544	558	552	552	552	552	552	552	552	552	552	552	553	553	553	553	553	554	554	554	554	554	555	555
Carcass ID Number	352	353	299	312	362	372	382	303	331	334	355	337	381	315	317	318	443	445	070	080	090	101	112	255	566
	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Hemangiosarcoma		X																							
Thecoma malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
Leiomyosarcoma	X																								
Polyp stromal								X																	
Sarcoma stromal					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	M	M	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	M	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other, trichoepithelioma																							X		
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X		X		X				X								
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple						X																			
Carcinoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 5 5 5 6 0 0 0 0 4 5 7 8 9 0 2 3 4 6 9 4 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Genital System		
Ovary	+ + + + + + + + + +	60
Adenoma		1
Hemangiosarcoma		1
Thecoma malignant		1
Uterus	+ + + + + + + + + +	60
Hemangiosarcoma		1
Leiomyosarcoma		1
Polyp stromal	X	6
Sarcoma stromal		1
Hematopoietic System		
Bone marrow	+ + + + + + + + + +	58
Lymph node	+ + + + + + + + + +	60
Lymph node, mandibular	+ + + + + + + + + +	60
Lymph node, mesenteric	+ + + + + + + + + +	59
Spleen	+ + + + + + + + + +	60
Hemangiosarcoma	X	1
Thymus	+ M + + + + + + + +	42
Integumentary System		
Mammary gland	+ + + M M + M + + +	44
Skin	+ + + + + + + + + +	60
Other, trichoepithelioma		1
Skin, control	+ + + + + + + + + +	60
Skin, site of application-no mass	+ + + + + + + + + +	60
Musculoskeletal System		
Bone	+ + + + + + + + + +	59
Nervous System		
Brain	+ + + + + + + + + +	60
Respiratory System		
Lung	+ + + + + + + + + +	60
Alveolar/bronchiolar adenoma	X	8
Alveolar/bronchiolar carcinoma		2
Alveolar/bronchiolar carcinoma, multiple		2
Carcinoma		1
Nose	+ + + + + + + + + +	60
Trachea	+ + + + + + + + + +	58

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 80 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6	
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 5 5 5 6 0 0 0 0 4 5 7 8 9 0 2 3 4 6 9 4 1 1 1 1 1 1 1 1 1 1	Total Tissues/ Tumors
Special Senses System		
Eye		1
Urinary System		
Kidney	+ + + + + + + + + +	60
Urinary bladder	+ + + + + + + + + +	56
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	60
Lymphoma malignant histiocytic		2
Lymphoma malignant lymphocytic	X	1
Lymphoma malignant mixed	X	1
Lymphoma malignant undifferentiated cell type		2

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg

Number of Days on Study	0 8 4	4 0 5	4 1 1	4 4 3	4 5 4	4 5 8	4 6 3	4 6 8	4 7 0	4 7 3	4 7 5	4 7 5	4 7 5	4 8 0	4 8 6	4 9 2	4 9 7	5 0 0	5 0 6	5 0 7	5 0 8	5 0 9	5 1 7	5 2 1	5 2 4
Carcass ID Number	4 3 3 1	4 8 0 1	4 4 6 1	4 4 3 1	4 5 6 1	4 5 2 1	4 2 7 1	4 5 5 1	4 6 4 1	4 3 1 1	4 2 2 1	4 2 4 1	4 5 3 1	4 4 5 1	4 2 3 1	4 3 6 1	4 5 8 1	4 6 2 1	4 7 8 1	4 4 9 1	4 4 2 1	4 7 3 1	4 3 0 1	4 6 5 1	4 4 4 1	4 6 1 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	M
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	A	M	+	+	+	+	+	A	+	+	A	+	+	M	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Hemangiosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Sarcoma, metastatic																									
Mesentery																						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	A	M	M	+	+	+	+	M	+	+	M	M	M	M	M	+	M	M	M	M	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X																						

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 3 1	5 3 1	5 3 2	5 3 2	5 4 2	5 4 5	5 4 6	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 4	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 6	5 5 6
Carcass ID Number	4 5 4 1	4 7 4 1	4 4 1 1	4 7 0 1	4 3 8 1	4 7 9 1	4 2 6 1	4 4 7 1	4 4 8 1	4 5 0 1	4 7 5 1	4 7 6 1	4 7 7 1	4 5 1 1	4 2 1 1	4 2 5 1	4 2 8 1	4 2 9 1	4 3 2 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 3 4 1	4 3 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Sarcoma, metastatic															X										
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma															X										
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	M	+	+	M	M	+	M	M	+	+	+	M	M	+	M	M	M	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6	
Carcass ID Number	4 4 4 4 4 4 4 4 4 3 4 4 5 5 6 6 7 7 9 0 2 7 9 0 9 1 3 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ + + + + + + + +	58
Gallbladder	+ + + + + + + + +	53
Intestine large	+ + + + + + + + +	59
Intestine large, cecum	+ + + + + + + + +	55
Intestine large, colon	M + + + + + + + +	56
Intestine large, rectum	+ + + + + + + + +	58
Intestine small	+ + + + + + + + +	59
Intestine small, duodenum	+ + + + + + + + +	52
Intestine small, ileum	+ + + + + + + + +	55
Intestine small, jejunum	+ + + + + + + + +	54
Hemangiosarcoma		1
Liver	+ + + + + + + + +	59
Hemangiosarcoma		1
Sarcoma, metastatic		1
Mesentery		1
Pancreas	+ + + + + + + + +	59
Salivary glands	+ + + + + + + + +	59
Stomach	+ + + + + + + + +	59
Stomach, forestomach	+ + + + + + + + +	59
Papilloma squamous		2
Stomach, glandular	+ + + + + + + + +	59
Sarcoma		1
Cardiovascular System		
Heart	+ + + + + + + + +	59
Endocrine System		
Adrenal gland	+ + + + + + + + +	59
Adrenal gland, cortex	+ + + + + + + + +	59
Adrenal gland, medulla	+ + + + + + + + +	59
Islets, pancreatic	+ + + + + + + + +	59
Parathyroid gland	+ M + M M + M M +	24
Pituitary gland	+ + + + M + + + +	55
Thyroid gland	+ + + + + + M + +	58
Follicular cell, adenoma		1

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg (continued)

Number of Days on Study	0	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5
	8	0	1	4	5	5	6	6	7	7	7	7	7	8	8	9	9	0	0	0	0	0	1	2	2
	4	5	1	3	4	8	3	8	0	3	5	5	5	0	6	2	7	0	6	7	8	9	7	1	4
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	3	8	4	4	5	5	2	5	6	3	2	2	5	4	2	3	5	6	7	4	7	3	6	4	6
	3	0	6	3	6	2	7	5	4	1	2	4	3	5	3	6	8	2	8	9	2	0	5	4	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Leiomyosarcoma																	X								
Polyp stromal																									
Sarcoma stromal																							X		
Schwannoma malignant													X												
Cervix, fibroma																									
Vagina																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	I	+	+	+	I	+	+	+	+	+	I	M	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	M	+	M	M	M	+	+	+	+	M	M	+	+	M	+	+	M	+	+	M	+
Adenocarcinoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	3	3	3	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	1	2	2	2	5	6	2	2	2	2	2	2	4	5	5	5	5	5	5	5	5	5	6	6	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	7	4	7	3	7	2	4	4	5	7	7	7	5	2	2	2	2	3	6	6	6	6	3	3	
	4	4	1	0	8	9	6	7	8	0	5	6	7	1	1	5	8	9	2	3	6	7	8	4	7	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																										
Tissue NOS			+																							
Genital System																										
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma				X																						
Uterus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leiomyoma																									X	
Leiomyosarcoma																										
Polyp stromal								X																		
Sarcoma stromal	X														X											
Schwannoma malignant																										
Cervix, fibroma																										
Vagina															+											
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma									X																	
Thymus	M	+	M	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	
Integumentary System																										
Mammary gland	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	
Adenocarcinoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skin, control	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skin, site of application-no mass	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg (continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6	
Carcass ID Number	4 4 4 4 4 4 4 4 4 3 4 4 5 5 6 6 7 7 9 0 2 7 9 0 9 1 3 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
General Body System		
Tissue NOS		1
Genital System		
Ovary	+ + + + + + + + +	58
Adenoma		1
Uterus	+ + + + + + + + +	58
Leiomyoma		1
Leiomyosarcoma		1
Polyp stromal		1
Sarcoma stromal		3
Schwannoma malignant	X	2
Cervix, fibroma	X	1
Vagina		1
Hematopoietic System		
Bone marrow	+ + + + + + + + +	59
Lymph node	+ + + + + + + + +	59
Lymph node, mandibular	+ + + + + + + + +	59
Lymph node, mesenteric	+ + + + + + + + +	57
Spleen	+ + + + + + + + +	59
Hemangiosarcoma		1
Thymus	+ + M + + + + + +	46
Integumentary System		
Mammary gland	+ + + + M + + + +	41
Adenocarcinoma		1
Skin	+ + + + + + + + +	59
Skin, control	+ + + + + + + + +	59
Skin, site of application-no mass	+ + + + + + + + +	59
Musculoskeletal System		
Bone	+ + + + + + + + +	59
Nervous System		
Brain	+ + + + + + + + +	59

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	0	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	
	8	0	1	4	5	5	6	6	7	7	7	7	7	8	8	9	9	0	0	0	0	0	1	2	2	
	4	5	1	3	4	8	3	8	0	3	5	5	5	0	6	2	7	0	6	7	8	9	7	1	4	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	3	8	4	4	5	5	2	5	6	3	2	2	5	4	2	3	5	6	7	4	7	3	6	4	6	
	3	0	6	3	6	2	7	5	4	1	2	4	3	5	3	6	8	2	8	9	2	0	5	4	1	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma					X																		X			
Alveolar/bronchiolar carcinoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye								+																		
Harderian gland								+																		
Adenoma								X																		
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant histiocytic							X																			
Lymphoma malignant mixed														X												

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg (continued)

Number of Days on Study	5 3 1	5 3 1	5 3 2	5 3 2	5 4 2	5 4 5	5 4 6	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 2	5 5 4	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	5 5 6	5 5 6
Carcass ID Number	4 5 4 1	4 7 4 1	4 4 1 1	4 7 0 1	4 3 8 1	4 7 9 1	4 2 6 1	4 4 7 1	4 4 8 1	4 5 0 1	4 7 5 1	4 7 6 1	4 7 7 1	4 5 1 1	4 2 1 1	4 2 5 1	4 2 8 1	4 2 9 1	4 3 2 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 3 4 1	4 3 7 1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X									X									X	
Alveolar/bronchiolar carcinoma										X		X					X			X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																										
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																										
Lymphoma malignant mixed																										

TABLE B2
Individual Animal Tumor Pathology of Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol: 160 mg/kg
(continued)

Number of Days on Study	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6	
Carcass ID Number	4 4 4 4 4 4 4 4 4 3 4 4 5 5 6 6 7 7 9 0 2 7 9 0 9 1 3 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Respiratory System		
Lung	+ + + + + + + + +	59
Alveolar/bronchiolar adenoma	X	6
Alveolar/bronchiolar carcinoma	X	5
Nose	+ + + + + + + + +	59
Trachea	+ + + + + + + + +	58
Special Senses System		
Eye		1
Harderian gland	+	2
Adenoma	X	2
Urinary System		
Kidney	+ + + + + + + + +	59
Urinary bladder	+ + + + + + + + +	56
Systemic Lesions		
Multiple organs	+ + + + + + + + +	59
Lymphoma malignant histiocytic		1
Lymphoma malignant mixed		1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rates[a]	7/60 (12%)	8/60 (13%)	8/60 (13%)	6/60 (10%)
Adjusted rates[b]	16.7%	22.3%	19.9%	18.0%
Terminal rates[c]	4/35 (11%)	2/26 (8%)	5/33 (15%)	3/27 (11%)
First incidence (days)	438	449	446	454
Life table tests[d]	P=0.476N	P=0.360	P=0.479	P=0.609N
Logistic regression tests[d]	P=0.403N	P=0.491	P=0.500	P=0.501N
Cochran-Armitage test[d]	P=0.407N			
Fisher exact test[d]		P=0.500	P=0.500	P=0.500N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	4/60 (7%)	0/60 (0%)	4/60 (7%)	5/60 (8%)
Adjusted rates	11.4%	0.0%	9.0%	18.5%
Terminal rates	4/35 (11%)	0/26 (0%)	1/33 (3%)	5/27 (19%)
First incidence (days)	552 (T)	–[e]	427	552 (T)
Life table tests	P=0.154	P=0.106N	P=0.631	P=0.338
Logistic regression tests	P=0.205	P=0.106N	P=0.632N	P=0.338
Cochran-Armitage test	P=0.206			
Fisher exact test		P=0.059N	P=0.641N	P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	11/60 (18%)	9/60 (15%)	12/60 (20%)	11/60 (18%)
Adjusted rates	27.4%	24.1%	28.8%	35.1%
Terminal rates	8/35 (23%)	2/26 (8%)	7/33 (21%)	8/27 (30%)
First incidence (days)	438	449	427	454
Life table tests	P=0.366	P=0.589N	P=0.473	P=0.395
Logistic regression tests	P=0.475	P=0.426N	P=0.517	P=0.576
Cochran-Armitage test	P=0.466			
Fisher exact test		P=0.404N	P=0.500	P=0.593N
Lung: Alveolar/bronchiolar Carcinoma or Adenosquamous Carcinoma				
Overall rates	4/60 (7%)	1/60 (2%)	5/60 (8%)	5/60 (8%)
Adjusted rates	11.4%	2.4%	11.9%	18.5%
Terminal rates	4/35 (11%)	0/26 (0%)	2/33 (6%)	5/27 (19%)
First incidence (days)	552 (T)	497	427	552 (T)
Life table tests	P=0.191	P=0.260N	P=0.486	P=0.338
Logistic regression tests	P=0.250	P=0.211N	P=0.516	P=0.338
Cochran-Armitage test	P=0.249			
Fisher exact test		P=0.182N	P=0.500	P=0.500
Uterus: Stromal Polyp				
Overall rates	4/60 (7%)	2/60 (3%)	6/60 (10%)	1/60 (2%)
Adjusted rates	10.4%	6.5%	14.3%	3.7%
Terminal rates	3/35 (9%)	1/26 (4%)	2/33 (6%)	1/27 (4%)
First incidence (days)	463	500	401	552 (T)
Life table tests	P=0.277N	P=0.448N	P=0.368	P=0.245N
Logistic regression tests	P=0.231N	P=0.359N	P=0.375	P=0.186N
Cochran-Armitage test	P=0.235N			
Fisher exact test		P=0.340N	P=0.372	P=0.182N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Uterus: Stromal Sarcoma				
Overall rates	1/60 (2%)	2/60 (3%)	1/60 (2%)	3/60 (5%)
Adjusted rates	2.0%	5.9%	3.0%	9.1%
Terminal rates	0/35 (0%)	1/26 (4%)	1/33 (3%)	1/27 (4%)
First incidence (days)	475	482	552 (T)	517
Life table tests	P=0.218	P=0.461	P=0.754	P=0.283
Logistic regression tests	P=0.240	P=0.502	P=0.762	P=0.305
Cochran-Armitage test	P=0.238			
Fisher exact test		P=0.500	P=0.752N	P=0.309
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	5/60 (8%)	4/60 (7%)	7/60 (12%)	4/60 (7%)
Adjusted rates	12.2%	12.2%	17.1%	12.6%
Terminal rates	3/35 (9%)	2/26 (8%)	3/33 (9%)	2/27 (7%)
First incidence (days)	463	482	401	517
Life table tests	P=0.556N	P=0.615N	P=0.375	P=0.586N
Logistic regression tests	P=0.495N	P=0.513N	P=0.383	P=0.505N
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.500N	P=0.381	P=0.500N
All Organs: Hemangiosarcoma				
Overall rates	0/60 (0%)	1/60 (2%)	3/60 (5%)	3/60 (5%)
Adjusted rates	0.0%	1.9%	8.5%	11.1%
Terminal rates	0/35 (0%)	0/26 (0%)	1/33 (3%)	3/27 (11%)
First incidence (days)	–	450	545	552 (T)
Life table tests	P=0.052	P=0.500	P=0.121	P=0.079
Logistic regression tests	P=0.067	P=0.494	P=0.126	P=0.079
Cochran-Armitage test	P=0.068			
Fisher exact test		P=0.500	P=0.122	P=0.122
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	4/60 (7%)	2/60 (3%)	5/60 (8%)	2/60 (3%)
Adjusted rates	9.4%	4.0%	13.8%	4.0%
Terminal rates	2/35 (6%)	0/26 (0%)	3/33 (9%)	0/27 (0%)
First incidence (days)	373	449	507	463
Life table tests	P=0.408N	P=0.391N	P=0.487	P=0.379N
Logistic regression tests	P=0.371N	P=0.333N	P=0.505	P=0.338N
Cochran-Armitage test	P=0.368N			
Fisher exact test		P=0.340N	P=0.500	P=0.340N
All Organs: Benign Neoplasms				
Overall rates	15/60 (25%)	10/60 (17%)	15/60 (25%)	14/60 (23%)
Adjusted rates	34.1%	28.8%	34.8%	37.5%
Terminal rates	9/35 (26%)	4/26 (15%)	8/33 (24%)	7/27 (26%)
First incidence (days)	370	449	401	411
Life table tests	P=0.380	P=0.372N	P=0.554	P=0.489
Logistic regression tests	P=0.484	P=0.194N	P=0.579	P=0.500N
Cochran-Armitage test	P=0.479			
Fisher exact test		P=0.184N	P=0.583N	P=0.500N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
All Organs: Malignant Neoplasms				
Overall rates	13/60 (22%)	8/60 (13%)	16/60 (27%)	17/60 (28%)
Adjusted rates	30.9%	18.2%	36.0%	46.6%
Terminal rates	8/35 (23%)	1/26 (4%)	7/33 (21%)	10/27 (37%)
First incidence (days)	373	375	427	463
Life table tests	P=0.070	P=0.300N	P=0.331	P=0.140
Logistic regression tests	P=0.097	P=0.166N	P=0.349	P=0.259
Cochran-Armitage test	P=0.096			
Fisher exact test		P=0.168N	P=0.335	P=0.264
All Organs: Benign and Malignant Neoplasms				
Overall rates	25/60 (42%)	16/60 (27%)	28/60 (47%)	26/60 (43%)
Adjusted rates	52.0%	39.9%	56.8%	63.9%
Terminal rates	14/35 (40%)	5/26 (19%)	13/33 (39%)	14/27 (52%)
First incidence (days)	120	375	401	411
Life table tests	P=0.152	P=0.228N	P=0.356	P=0.273
Logistic regression tests	P=0.218	P=0.058N	P=0.317	P=0.500
Cochran-Armitage test	P=0.217			
Fisher exact test		P=0.062N	P=0.357	P=0.500

(T) Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol[a]

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
Early deaths				
Accident				1
Moribund	20	27	22	25
Natural deaths	5	7	5	7
Survivors				
Terminal sacrifice	35	26	33	27
Animals examined microscopically	60	60	60	59
Alimentary System				
Esophagus	(59)	(59)	(59)	(58)
Amyloid deposition		2 (3%)	3 (5%)	1 (2%)
Gallbladder	(53)	(53)	(56)	(53)
Cyst			1 (2%)	
Intestine large, cecum	(57)	(56)	(59)	(55)
Amyloid deposition			1 (2%)	1 (2%)
Polyarteritis	1 (2%)			
Intestine large, colon	(56)	(56)	(58)	(56)
Amyloid deposition	1 (2%)		1 (2%)	1 (2%)
Edema	2 (4%)		3 (5%)	
Polyarteritis				1 (2%)
Intestine large, rectum	(57)	(55)	(54)	(58)
Amyloid deposition			1 (2%)	1 (2%)
Intestine small, duodenum	(58)	(56)	(57)	(52)
Amyloid deposition	24 (41%)	23 (41%)	16 (28%)	19 (37%)
Intestine small, ileum	(57)	(57)	(60)	(55)
Amyloid deposition	37 (65%)	45 (79%)	41 (68%)	37 (67%)
Edema			2 (3%)	
Hyperplasia, lymphoid				1 (2%)
Mucosa, inflammation, focal		1 (2%)		
Intestine small, jejunum	(55)	(54)	(56)	(54)
Amyloid deposition	25 (45%)	30 (56%)	20 (36%)	28 (52%)
Liver	(60)	(60)	(60)	(59)
Amyloid deposition	30 (50%)	37 (62%)	27 (45%)	33 (56%)
Angiectasis, focal	1 (2%)	1 (2%)		
Clear cell focus				1 (2%)
Hematopoietic cell proliferation	2 (3%)	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)			
Infiltration cellular, lymphocyte, focal			1 (2%)	
Inflammation, chronic, focal	24 (40%)	21 (35%)	24 (40%)	23 (39%)
Necrosis	2 (3%)			1 (2%)
Necrosis, focal	1 (2%)	2 (3%)	6 (10%)	3 (5%)
Centrilobular, hypertrophy				1 (2%)
Mesentery	(1)		(2)	(1)
Hemorrhage, focal				1 (100%)
Polyarteritis			1 (50%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Alimentary System (continued)				
Pancreas	(60)	(57)	(60)	(59)
Edema			1 (2%)	
Focal cellular change	2 (3%)	1 (2%)	1 (2%)	3 (5%)
Necrosis, focal		1 (2%)		
Polyarteritis				1 (2%)
Acinus, amyloid deposition	2 (3%)	1 (2%)	1 (2%)	
Acinus, hypertrophy, focal	2 (3%)	1 (2%)	6 (10%)	
Interlobular, edema	15 (25%)	15 (26%)	14 (23%)	15 (25%)
Salivary glands	(60)	(59)	(60)	(59)
Amyloid deposition	27 (45%)	29 (49%)	32 (53%)	32 (54%)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, suppurative, focal			1 (2%)	
Interlobular, edema	18 (30%)	21 (36%)	8 (13%)	11 (19%)
Stomach, forestomach	(60)	(60)	(60)	(59)
Ulcer				1 (2%)
Submucosa, inflammation, subacute				1 (2%)
Stomach, glandular	(60)	(59)	(60)	(59)
Amyloid deposition	5 (8%)		1 (2%)	3 (5%)
Necrosis	1 (2%)			
Epithelium, vacuolization cytoplasmic	1 (2%)			
Mucosa, degeneration			2 (3%)	
Mucosa, necrosis, focal			1 (2%)	
Cardiovascular System				
Heart	(60)	(60)	(60)	(59)
Amyloid deposition	37 (62%)	35 (58%)	33 (55%)	31 (53%)
Fibrosis		1 (2%)		
Inflammation, acute		1 (2%)		
Necrosis, focal		1 (2%)		
Polyarteritis			3 (5%)	1 (2%)
Atrium, inflammation, suppurative				1 (2%)
Atrium, thrombus	6 (10%)	5 (8%)	3 (5%)	3 (5%)
Myocardium, inflammation, suppurative, focal				1 (2%)
Endocrine System				
Adrenal gland	(60)	(59)	(60)	(59)
Capsule, hyperplasia	56 (93%)	54 (92%)	58 (97%)	54 (92%)
Corticomedullary junction, amyloid deposition	37 (62%)	40 (68%)	31 (52%)	33 (56%)
Corticomedullary junction, hemorrhage	2 (3%)	1 (2%)		
Corticomedullary junction, pigmentation	37 (63%)	34 (58%)	38 (63%)	33 (56%)
Corticomedullary junction, vacuolization cytoplasmic	6 (10%)	9 (15%)	5 (8%)	5 (8%)
Adrenal gland, cortex	(60)	(59)	(60)	(59)
Amyloid deposition	1 (2%)			
Fibrosis, focal			1 (2%)	
Hematopoietic cell proliferation				2 (3%)
Hypertrophy, focal	2 (3%)			1 (2%)
Necrosis		1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Endocrine System (continued)				
Adrenal gland, medulla	(59)	(58)	(59)	(59)
Hyperplasia, focal	1 (2%)		1 (2%)	
Parathyroid gland	(34)	(30)	(30)	(24)
Amyloid deposition	12 (35%)	14 (47%)	15 (50%)	8 (33%)
Cyst			1 (3%)	
Pituitary gland	(54)	(56)	(54)	(55)
Necrosis			1 (2%)	
Pars distalis, cyst	3 (6%)		2 (4%)	3 (5%)
Pars distalis, hyperplasia, focal	1 (2%)	1 (2%)	3 (6%)	
Thyroid gland	(58)	(58)	(56)	(58)
Amyloid deposition	23 (40%)	26 (45%)	22 (39%)	17 (29%)
Inflammation, acute			1 (2%)	
Inflammation, chronic	1 (2%)	2 (3%)	1 (2%)	2 (3%)
C-cell, hyperplasia				1 (2%)
Follicle, dilatation	8 (14%)	7 (12%)	6 (11%)	10 (17%)
Follicular cell, hyperplasia	4 (7%)	8 (14%)	5 (9%)	9 (16%)
General Body System				
Tissue NOS		(1)	(1)	(1)
Granuloma				1 (100%)
Genital System				
Ovary	(60)	(57)	(60)	(58)
Abscess	1 (2%)			1 (2%)
Amyloid deposition	20 (33%)	21 (37%)	27 (45%)	30 (52%)
Atrophy	13 (22%)	14 (25%)	16 (27%)	10 (17%)
Congestion		1 (2%)		
Cyst	6 (10%)	10 (18%)	9 (15%)	13 (22%)
Hematocyst		2 (4%)		1 (2%)
Hemorrhage	2 (3%)	3 (5%)	1 (2%)	3 (5%)
Bilateral, hemorrhage	1 (2%)		1 (2%)	
Follicle, cyst				1 (2%)
Periovarian tissue, cyst	13 (22%)	9 (16%)	8 (13%)	11 (19%)
Uterus	(60)	(58)	(60)	(58)
Abscess			1 (2%)	1 (2%)
Amyloid deposition	3 (5%)	2 (3%)	1 (2%)	1 (2%)
Angiectasis, focal			1 (2%)	
Congestion	1 (2%)			
Hemorrhage			1 (2%)	
Hyperplasia	1 (2%)			
Cervix, cyst	1 (2%)			
Cervix, hypertrophy	1 (2%)			1 (2%)
Cervix, inflammation, subacute				1 (2%)
Endometrium, hyperplasia, cystic	55 (92%)	57 (98%)	58 (97%)	56 (97%)
Myometrium, degeneration		1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Hematopoietic System				
Bone marrow	(59)	(60)	(58)	(59)
Calvarium, myelofibrosis	4 (7%)	2 (3%)		1 (2%)
Sternal, myelofibrosis	4 (7%)	2 (3%)	7 (12%)	2 (3%)
Lymph node	(60)	(60)	(60)	(59)
Hyperplasia			1 (2%)	
Renal, hyperplasia				1 (2%)
Lymph node, mandibular	(57)	(60)	(60)	(59)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, plasma cell	1 (2%)			1 (2%)
Necrosis				1 (2%)
Lymph node, mesenteric	(60)	(57)	(59)	(57)
Abscess	1 (2%)			
Amyloid deposition	1 (2%)	2 (4%)	3 (5%)	3 (5%)
Granuloma		1 (2%)		1 (2%)
Hyperplasia		1 (2%)		3 (5%)
Hyperplasia, lymphoid	2 (3%)	1 (2%)		3 (5%)
Lymphocyte, necrosis			1 (2%)	
Spleen	(60)	(60)	(60)	(59)
Amyloid deposition	25 (42%)	23 (38%)	22 (37%)	19 (32%)
Hematopoietic cell proliferation	55 (93%)	52 (87%)	56 (93%)	55 (93%)
Hyperplasia, lymphoid	2 (3%)	2 (3%)		2 (3%)
Pigmentation, hemosiderin	22 (37%)	27 (45%)	17 (28%)	24 (41%)
Capsule, hyperplasia, focal		1 (2%)		
Thymus	(47)	(49)	(42)	(46)
Amyloid deposition			1 (2%)	
Depletion lymphoid		1 (2%)		
Integumentary System				
Mammary gland	(38)	(43)	(44)	(41)
Hyperplasia	3 (8%)	2 (5%)	2 (5%)	1 (2%)
Hyperplastic alveolar nodule	5 (13%)	4 (9%)	1 (2%)	4 (10%)
Inflammation, chronic			1 (2%)	
Lactation	1 (3%)			
Duct, hyperplasia		1 (2%)		
Skin	(60)	(60)	(60)	(59)
Edema			1 (2%)	
Abdominal, dermis, inflammation, chronic		3 (5%)	1 (2%)	1 (2%)
Abdominal, subcutaneous tissue, edema	18 (30%)	27 (45%)	17 (28%)	20 (34%)
Face, acanthosis	1 (2%)			
Forelimb, ulcer	1 (2%)			
Head, ulcer		1 (2%)		
Neck, ulcer		1 (2%)		1 (2%)
Other, inflammation, chronic	1 (2%)			
Tail, abscess		1 (2%)		
Thoracic, acanthosis	1 (2%)			
Thoracic, ventral, acanthosis	1 (2%)			
Thoracic, ventral, exudate	1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Integumentary System (continued)				
Skin, control	(60)	(60)	(60)	(59)
Exudate	1 (2%)			
Hyperkeratosis				1 (2%)
Dermis, inflammation, chronic	3 (5%)	2 (3%)	3 (5%)	
Subcutaneous tissue, edema	8 (13%)	15 (25%)	12 (20%)	9 (15%)
Skin, site of application-no mass	(60)	(60)	(60)	(59)
Acanthosis	4 (7%)	1 (2%)		1 (2%)
Exudate, focal			1 (2%)	
Hyperkeratosis	2 (3%)			1 (2%)
Ulcer	3 (5%)			1 (2%)
Dermis, inflammation, chronic	11 (18%)	9 (15%)	2 (3%)	7 (12%)
Subcutaneous tissue, edema	3 (5%)	9 (15%)	2 (3%)	6 (10%)
Musculoskeletal System				
None				
Nervous System				
Brain	(60)	(60)	(60)	(59)
Hemorrhage, focal			1 (2%)	
Thalamus, mineralization, focal	15 (25%)	17 (28%)	9 (15%)	13 (22%)
Respiratory System				
Lung	(60)	(60)	(60)	(59)
Congestion	2 (3%)	3 (5%)	4 (7%)	2 (3%)
Hemorrhage		2 (3%)		2 (3%)
Infiltration cellular, lymphocyte, focal	1 (2%)			
Inflammation, chronic, focal	12 (20%)	9 (15%)	14 (23%)	4 (7%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (2%)		1 (2%)
Alveolus, infiltration cellular, histiocyte, focal	4 (7%)	2 (3%)	2 (3%)	6 (10%)
Artery, amyloid deposition			1 (2%)	
Interstitium, inflammation, chronic	5 (8%)	5 (8%)	1 (2%)	7 (12%)
Nose	(60)	(59)	(60)	(59)
Exudate				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative		1 (2%)		
Glands, hyperplasia, focal			1 (2%)	
Nasolacrimal duct, inflammation, suppurative	1 (2%)			
Septum, amyloid deposition			1 (2%)	
Special Senses System				
Ear	(2)			
Bilateral, ulcer	1 (50%)			
Eye			(1)	(1)
Anterior chamber, hemorrhage				1 (100%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 18-Month Dermal Study of *p*-Nitrophenol (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	160 mg/kg
Urinary System				
Kidney	(60)	(60)	(60)	(59)
Abscess				1 (2%)
Amyloid deposition	39 (65%)	45 (75%)	42 (70%)	41 (69%)
Hydronephrosis			1 (2%)	1 (2%)
Hypertrophy	1 (2%)			
Infarct	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte, focal	1 (2%)			
Inflammation, suppurative	1 (2%)			
Metaplasia, osseous			1 (2%)	
Nephropathy	5 (8%)	4 (7%)	2 (3%)	5 (8%)
Capsule, inflammation, focal			1 (2%)	
Cortex, atrophy			1 (2%)	
Cortex, atrophy, focal	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Cortex, cyst		3 (5%)	2 (3%)	1 (2%)
Cortex, renal tubule, mineralization, focal			1 (2%)	
Pelvis, dilatation	1 (2%)	2 (3%)		3 (5%)
Proximal convoluted renal tubule, degeneration, hyaline	1 (2%)			
Urethra		(1)		
Bulbourethral gland, dilatation		1 (100%)		
Urinary bladder	(57)	(54)	(56)	(56)
Amyloid deposition	5 (9%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocyte, focal	1 (2%)			

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

APPENDIX C
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). *p*-Nitrophenol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). *p*-Nitrophenol was incubated with the *Salmonella typhimurium* tester strain (TA100, TA1535, TA1537, TA98) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of *p*-nitrophenol. High dose was limited by toxicity. All trials were repeated.

A positive response in this assay is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response is considered negative when no increase in revertant colonies is observed following chemical treatment.

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is presented briefly below. *p*-Nitrophenol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). *p*-Nitrophenol was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each trial consisted of concurrent solvent and positive controls and of at least three doses of *p*-nitrophenol; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with *p*-nitrophenol in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing *p*-nitrophenol was removed and replaced with fresh medium containing BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with *p*-nitrophenol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no *p*-nitrophenol, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining procedures were the same as for cells treated without S9. For the SCE test, because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with *p*-nitrophenol for 19 hours; Colcemid was added and incubation continued for 2 to 3 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *p*-nitrophenol and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 19.5 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test

was based on the cell cycle information obtained in the SCE test: because cell cycle delay was anticipated, the incubation period was extended from the standard 10 to 12 hour period.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; usually 100 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Abs data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

Drosophila Protocol

The assays for induction of mutations were performed as described in Zimmering *et al.* (1985). *p*-Nitrophenol was supplied as a coded aliquot from Radian Corporation (Austin, TX). Initially, *p*-nitrophenol was assayed in the sex-linked recessive lethal (SLRL) test by feeding for three days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, *p*-nitrophenol was retested by injection into adult males.

To administer *p*-nitrophenol by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double stick tape; *p*-nitrophenol was injected into the thorax under the wing with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of *p*-nitrophenol at a level which would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10 to 20 flies per vial) to feed for 72 hours on a solution of *p*-nitrophenol in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of *p*-nitrophenol dissolved in 0.7% NaCl and were allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier post-meiotic stages. F_1 heterozygous females were allowed to mate with their siblings and were then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution). Presumptive lethal mutations were identified as occurring in vials containing no wild-type males after 17 days; these were retested. The feeding and injection experiments combined

resulted in the testing of over 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was not run.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if a) the P value was between 0.01 and 0.05 but the frequency in the treatment group was between 0.10% and 0.15%, or b) the P value was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

RESULTS

p-Nitrophenol (10 to 3,333 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983) (Table C1). A weakly positive response was observed in one trial with strain TA98 in the presence of hamster S9, but it was not repeated in a second trial. In cytogenetic tests with CHO cells, *p*-nitrophenol did not induce SCE, with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table C2). In the first trial conducted with S9, a weakly positive response was observed at the highest nonlethal dose tested (500 μg/mL), but this response was not reproduced in a second trial performed with higher doses of *p*-nitrophenol and the assay was concluded to be negative. *p*-Nitrophenol induced cell cycle delay and harvest times had to be extended for most cultures to ensure adequate numbers of cells for analysis. In the Abs test with CHO cells, *p*-nitrophenol was negative in the absence of S9, but with S9, a significant increase in aberrations was observed in each of two trials at concentrations which induced cell cycle delay (Table C3). *p*-Nitrophenol was negative for induction of sex-linked recessive lethal mutations in the germ cells of male *Drosophila melanogaster* administered *p*-nitrophenol by feeding (up to 7,500 ppm) or by injection (up to 1,500 ppm) (Table C4; Zimmering *et al.*, 1985).

TABLE C1
Mutagenicity of *p*-Nitrophenol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	149 ± 8.1	195 ± 5.9	192 ± 3.9	202 ± 2.7	182 ± 7.8	202 ± 7.8
	10	149 ± 16.3		184 ± 4.6		192 ± 6.1	
	33	140 ± 4.6		181 ± 11.3		184 ± 1.9	
	100	116 ± 7.1	172 ± 11.5	185 ± 3.4	216 ± 9.9	182 ± 17.6	221 ± 11.7
	166		165 ± 10.1		240 ± 7.1		224 ± 18.5
	333	103 ± 4.5	156 ± 7.5	198 ± 6.8	264 ± 10.1	205 ± 0.7	249 ± 7.8
	666		152 ± 4.0		241 ± 11.9		194 ± 11.4
	1,000	104 ± 7.8	144 ± 9.1	179 ± 3.2	142 ± 11.5	182 ± 14.3	157 ± 22.1
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Equivocal
Positive control[c]		464 ± 3.2	408 ± 1.9	847 ± 55.0	837 ± 53.6	424 ± 20.8	510 ± 25.8
TA1535	0	8 ± 2.0	10 ± 1.5	11 ± 2.5	12 ± 2.0	10 ± 1.5	10 ± 2.1
	10	6 ± 0.3		16 ± 1.8		13 ± 1.2	
	33	11 ± 1.8		8 ± 1.5		9 ± 1.5	
	100	12 ± 2.3	9 ± 2.3	14 ± 2.1	9 ± 2.1	15 ± 2.2	13 ± 1.2
	166		8 ± 2.0		9 ± 1.0		8 ± 1.5
	333	5 ± 2.0	7 ± 1.2	9 ± 1.5	6 ± 1.2	16 ± 1.7	10 ± 3.2
	666		14 ± 1.2		7 ± 1.2		8 ± 0.3
	1,000	7 ± 2.2	2 ± 0.3	10 ± 2.1	5 ± 0.3	10 ± 1.9	6 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		401 ± 54.9	305 ± 27.3	103 ± 9.4	55 ± 7.2	56 ± 11.5	76 ± 2.9
TA1537	0	4 ± 0.7	3 ± 1.5	7 ± 1.2	4 ± 0.3	8 ± 2.5	5 ± 1.5
	10	8 ± 2.7		12 ± 0.6		7 ± 1.0	
	33	5 ± 1.2		6 ± 2.3		8 ± 1.2	
	100	7 ± 0.7	9 ± 2.2	10 ± 1.8	7 ± 1.9	13 ± 2.1	6 ± 0.6
	166		8 ± 1.2		11 ± 0.9		9 ± 2.5
	333	9 ± 2.6	11 ± 2.7	22 ± 5.5	9 ± 1.5	10 ± 3.5	9 ± 1.2
	666		10 ± 2.1		7 ± 2.2		8 ± 1.2
	1,000	11 ± 1.8	7 ± 2.0	15 ± 3.8	–[d]	14 ± 3.2	1 ± 1.0
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		34 ± 7.7	38 ± 9.1	59 ± 0.7	19 ± 1.3	33 ± 9.5	21 ± 2.1
TA98	0	16 ± 2.4	17 ± 4.1	22 ± 3.8	23 ± 1.7	26 ± 2.0	25 ± 0.9
	10	12 ± 3.2		26 ± 2.4		30 ± 2.2	
	33	14 ± 1.2		26 ± 7.0		27 ± 1.5	
	100	23 ± 2.5	25 ± 3.0	20 ± 2.9	21 ± 2.4	28 ± 3.1	21 ± 1.7
	166		25 ± 6.0		19 ± 5.5		23 ± 2.3
	333	16 ± 2.3	33 ± 5.5	41 ± 9.5	27 ± 3.8	25 ± 3.5	24 ± 1.5
	666		27 ± 4.7		27 ± 4.4		21 ± 5.9
	1,000	15 ± 1.7	15 ± 0.3	49 ± 2.0	19 ± 2.2	33 ± 4.7	14 ± 1.7
Trial summary		Negative	Equivocal	Weakly Positive	Negative	Negative	Negative
Positive control		226 ± 7.0	216 ± 11.9	674 ± 32.6	346 ± 38.0	209 ± 9.8	209 ± 15.1

[a] Study performed at Case Western Reserve University. The detailed protocol and these data are presented in Haworth *et al.* (1983). The solvent control is 0 μg/plate dose.
[b] Revertants are presented as mean ± the standard error from three plates.
[c] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.
[d] Toxic

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrophenol[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
–S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,016	528	0.51	10.6	26.0	
Mitomycin-C	0.001	50	1,016	583	0.57	11.7	26.0	10.42
	0.010	5	106	171	1.61	34.2	26.0	210.42
p-Nitrophenol	0.167	50	1,014	558	0.55	11.2	31.5[c]	5.89
	0.500	50	1,019	618	0.60	12.4	31.5[c]	16.70
	1.700	0					31.5[c]	
							Trend:	2.619
							Probability:	0.004[d]
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,017	490	0.48	9.8	26.0	
Mitomycin-C	0.001	50	1,024	626	0.61	12.5	26.0	26.88
	0.010	5	104	219	2.10	43.8	26.0	337.06
p-Nitrophenol	5	50	1,017	536	0.52	10.7	33.5[c]	9.39
	10	50	1,023	529	0.51	10.6	33.5[c]	7.33
	25	50	1,002	529	0.52	10.6	33.5[c]	9.58
							Trend:	1.283
							Probability:	0.100
+S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,016	508	0.50	10.2	26.0	
Cyclophosphamide	0.4	50	1,023	774	0.75	15.5	26.0	51.32
	2.0	5	103	250	2.42	50.0	26.0	385.44
p-Nitrophenol	50	50	1,037	500	0.48	10.0	26.0	-3.57
	167	50	1,028	521	0.50	10.4	31.5[c]	1.36
	500	50	1,030	620	0.60	12.4	31.5[c]	20.39*
	1,700	0					31.5[c]	
							Trend:	3.253
							Probability:	0.001

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrophenol (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
+S9 (continued)								
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,026	475	0.46	9.5	26.0	
Cyclophosphamide	0.4	50	1,032	785	0.76	15.7	26.0	64.30
	2.0	5	104	184	1.76	36.8	26.0	282.16
p-Nitrophenol	1,000	50	1,023	458	0.44	9.2	26.0	-3.30
	1,300	50	1,026	500	0.48	10.0	26.0	5.26
	1,500	50	1,022	518	0.50	10.4	33.5[c]	9.48
	2,000	0						
								Trend: 1.780
								Probability: 0.038

[a] Positive (≥20% increase over solvent control)
[b] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987).
[c] Percent increase in SCEs/chromosome of culture exposed to *p*-nitrophenol relative to those of culture exposed to solvent.
[d] Because *p*-nitrophenol induced a delay in the cell division cycle, harvest time was extended as needed to maximize the proportion of second division cells available for analysis.
Significance of relative SCEs/chromosome by linear regression trend test vs. log of the dose

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *p*-Nitrophenol[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 21.5 hours Summary: Negative					**Trial 1** – Harvest time: 21.5 hours Summary: Weak positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	0	0.00	0.0		100	9	0.09	7.0
Mitomycin-C					Cyclophosphamide				
0.040	100	2	0.02	2.0	7.500	100	18	0.18	15.0
0.063	50	5	0.10	10.0	37.500	25	23	0.92	48.0
p-Nitrophenol					*p*-Nitrophenol				
100	100	5	0.05	4.0	1,500	100	4	0.04	4.0
250	100	0	0.00	0.0	1,750	100	13	0.13	8.0
500	100	1	0.01	1.0	2,000	20	11	0.55	30.0*
1,000	0				2,500	0			
			Trend: –0.267					Trend: 2.172	
			Probability: 0.605[b]					Probability: 0.015	
Trial 2 – Harvest time: 21.5 hours Summary: Negative					**Trial 2** – Harvest time: 21.5 hours Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	2	0.02	2.0		100	2	0.02	2.0
Mitomycin-C					Cyclophosphamide				
0.0400	100	12	0.12	12.0	6.250	100	11	0.11	10.0
0.0625	25	8	0.32	28.0	12.500	25	18	0.72	44.0
p-Nitrophenol					*p*-Nitrophenol				
100	100	0	0.00	0.0	1,250	100	8	0.08	5.0
250	100	0	0.00	0.0	1,500	50	25	0.50	22.0*
500	100	4	0.04	4.0	1,750	50	49	0.98	32.0*
750	0				2,000	0			
			Trend: 1.012					Trend: 6.042	
			Probability: 0.156					Probability: 0.000	

* Positive ($P<0.05$)
[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE C4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by *p*-Nitrophenol[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Total[b]
Study performed at University of Wisconsin, Madison							
Injection	1,500	37	12	0/2,178	2/1,664	0/1,382	2/5,224 (0.04%)
	0			2/2,499	2/1,882	4/1,460	8/5,841 (0.14%)
Feeding	2,500	12	0	1/2,258	0/1,578	1/1,728	2/5,564 (0.04%)
	0			1/2,202	0/1,678	1/1,817	2/5,697 (0.04%)
Study performed at Brown University							
Feeding	1,000	1	3	0/1,159	0/1,200	1/1,164	1/3,523 (0.03%)
	0			0/1,172	1/1,217	0/1,077	1/3,466 (0.03%)
Injection	1,000	39	16	3/3,304	1/3,467	2/3,278	6/10,049 (0.06%)
	0			7/3,385	4/3,389	1/3,650	12/10,424 (0.12%)
Feeding	6,000	53	0	1/1,744	2/1,767	0/1,748	3/5,259 (0.06%)
	0			1/1,779	0/1,795	2/1,757	3/5,331 (0.06%)
Feeding	7,500	47	0	0/579	1/593	1/495	2/1,667 (0.12%)
	0			0/567	0/593	0/492	0/1,652 (0.00%)

[a] A detailed protocol of the sex-linked recessive lethal assay and the data from the Brown University study are presented in Zimmering *et al.* (1985) and Margolin *et al.* (1983).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

APPENDIX D
COMPOUND-RELATED SKIN LESIONS IN SWISS-WEBSTER MICE

COMPOUND-RELATED SKIN LESIONS IN SWISS-WEBSTER MICE

13-WEEK STUDY SUMMARY

Doses of 0, 21.9, 43.8, 87.5, 175, and 350 mg/kg *p*-nitrophenol in acetone were applied to the interscapular skin of male and female Swiss-Webster mice on Monday, Wednesday, and Friday. All males and 8/10 females receiving 350 mg/kg and 3/10 males and 1/10 females receiving 175 mg/kg died prior to the end of the study. All deaths, except one, were considered to be related to the administration of *p*-nitrophenol. Epidermal necrosis, hyperplasia and hyperkeratosis, and skin inflammation were found in the 175 and 350 mg/kg males.

Epidermal hyperplasia and hyperkeratosis and skin inflammation were observed in the 350 mg/kg females (Table D1). Epidermal necrosis was slight to moderate in severity and was characterized by necrosis with indistinct, poorly stained cells well delineated from viable tissue by a peripheral zone of neutrophilic inflammatory cells. These lesions were focal and multifocal and extended into the dermis of all affected animals. Epidermal hyperplasia with hyperkeratosis ranged from minimal to marked in severity and were focal, multifocal to diffuse. The epidermal hyperplasia was characterized by increased numbers of squamous cells in all layers of the epidermis, greater than the normal 2 to 3 cell thickness. Epidermal hyperkeratosis was characterized by increased keratin on the epidermal surface resulting in thicknesses greater than that of the normal keratin layer; the keratin layer is usually less than the height of the basal cell layer of the skin.

Inflammation of several types, ranging from minimal to marked in severity, were focal, multifocal, and diffuse. The predominate features which occurred in various combinations were mixed inflammatory cell infiltrates of neutrophils, eosinophils, mast cells, and lymphoid cells usually loosely arranged deep in the dermis, cutaneous skeletal muscle, and adjacent subcutaneous tissue; accumulations of neutrophils at the border of necrotic tissues; superficial suppurative epidermitis with fibrinosuppurative and necrotic exudate; and subepithelial fibrosis.

TABLE D1
Incidences of Compound-Related Skin Lesions in Swiss-Webster Mice in the 13-Week Dermal Study of *p*-Nitrophenol[a]

Dose (mg/kg)	0.0	21.9	43.8	87.5	175.0	350.0
Male						
Skin/epidermis						
Hyperplasia	0	2 (2.0)[b]	1 (1.0)	0	5 (1.8)*	9 (2.1)**
Hyperkeratosis	0	2 (2.0)	2 (1.0)	1 (1.0)	5 (1.8)*	7 (1.8)**
Skin						
Inflammation	0	1 (4.0)	1 (1.0)	0	2 (1.5)	7 (2.0)**
Necrosis	0	0	1 (1.0)	0	2 (2.5)	3 (3.0)
Female						
Skin/epidermis						
Hyperplasia	2 (1.0)	3 (1.0)	1 (1.0)	5 (1.2)	3 (1.0)	7 (2.0)*
Hyperkeratosis	2 (1.0)	5 (1.0)	7 (1.0)*	7 (1.3)*	3 (1.0)	7 (2.1)*
Skin						
Inflammation	1 (1.0)	0	0	1 (2.0)	2 (1.0)	8 (2.4)**
Necrosis	0	0	0	0	0	0

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Ten animals examined for each tissue
[b] Values in parentheses are average severity grades for affected animals; severity grade of 1=minimal, 2=mild, 3=moderate.

APPENDIX E
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

p-Nitrophenol, manufactured by E.I. duPont de Nemours & Company, Incorporated (Wilmington, DE), was obtained in one lot (lot number 730). The bulk chemical was received by the study laboratory for the 18-month studies on July 19, 1984. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). Reports from MRI on the analyses performed in support of the *p*-nitrophenol studies are on file at the National Institute of Environmental Health Sciences.

The bulk chemical, a buff to tan colored, flaked crystalline solid, was identified as *p*-nitrophenol by its melting point and by infrared, ultraviolet, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with those reported in the literature for *p*-nitrophenol, as shown in Figures E1 and E2 (*Sadtler Standard Spectra*, 1976).

Purity was evaluated by elemental analysis, water analysis, potentiometric titration, and chromatographic analyses. Potentiometric titrations of the phenol group and the nitro group were performed. The acidic phenol proton was titrated with 0.1 N *t*-butylammonium hydroxide in isopropanol:methanol (9:1). The nitro group was reduced first with excess titanous chloride, then back titrated with ferric alum. Thin-layer chromatography (TLC) was performed on silica gel plates with two solvent systems using *p*-nitrophenetole as a standard reference. The two solvent systems were chloroform:ethyl acetate:acetic acid (91:7:3) and diethyl ether:hexanes (56:44). Visualization was achieved using ultraviolet (UV) light at 254 nm following treatment with Rhodamine B in 1% ethanol. High performance liquid chromatography (HPLC) was performed with a μBondpak C_{18} column with two solvent systems: water with 1% acetic acid (30%, isocratic) and methanol with 1% acetic acid (70%, isocratic). UV detection was at 313 nm.

The melting point for *p*-nitrophenol was determined to be from 110° C to 114.5° C, which was in agreement with melting point values of 113° C to 114° C found in the literature. Elemental analysis for carbon, hydrogen, nitrogen, and oxygen were within the theoretical values for *p*-nitrophenol. Water content of *p*-nitrophenol was 0.58% as determined by Karl Fischer analysis. Purity was 97.5% based on titration of the phenol group and 100.8% based on titration of the nitro group. Regardless of the solvent system used for TLC or HPLC, only one major spot or peak was detected, which suggested that no impurities were present within detectable limits. Based on the purity analysis data the purity was estimated at >97%.

The analytical chemistry laboratory found *p*-nitrophenol to be stable in bulk form when stored for 2 weeks at temperatures up to 60° C. The study laboratory stored the bulk chemical protected from light at 4° to 5° C. A sample of the bulk chemical was frozen and used as reference for comparison in determining the amount of degradation of the bulk chemical throughout the 18-month studies. The bulk chemical was analyzed by the study laboratory at 4-month intervals until the study was terminated; no degradation was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations for dermal application were prepared by slowly adding the appropriate amount of *p*-nitrophenol to acetone, Mallinckrodt analytical reagent grade (lot number 2440KVEZ) obtained from

American Scientific Products (Columbia, MD), and mixed by inversion (Table E1). Since the dose volume was a constant 100 μL, the formulation concentrations were changed over the course of the study to maintain the same mg/kg body weight dose. Determination of the dose concentration was by flame-ionization gas chromatography using *n*-undecanol as the internal standard and comparison to standard acetone solutions of *p*-nitrophenol. Linear regression analysis of the ratio of the *p*-nitrophenol peak to the internal standard was used to calculate the calibration curve. Stability study results from the analytical chemistry laboratory indicated that dose formulations of *p*-nitrophenol were stable for at least 3 weeks at room temperature protected from light. Once prepared, formulations were stored at −20° C in amber glass vials with Teflon®-lined caps until the week of dosing; thereafter, the formulations were kept at room temperature protected from light. Periodic analyses of the formulations for dermal application were conducted by the study laboratory and the analytical chemistry laboratory throughout the studies (Table E2). The determined concentrations of the dose formulations were consistently higher, but within 10% of the target concentrations. Samples submitted by the study laboratory for referee analysis were within 5% of the dose concentration determined by the referee laboratory (Table E3).

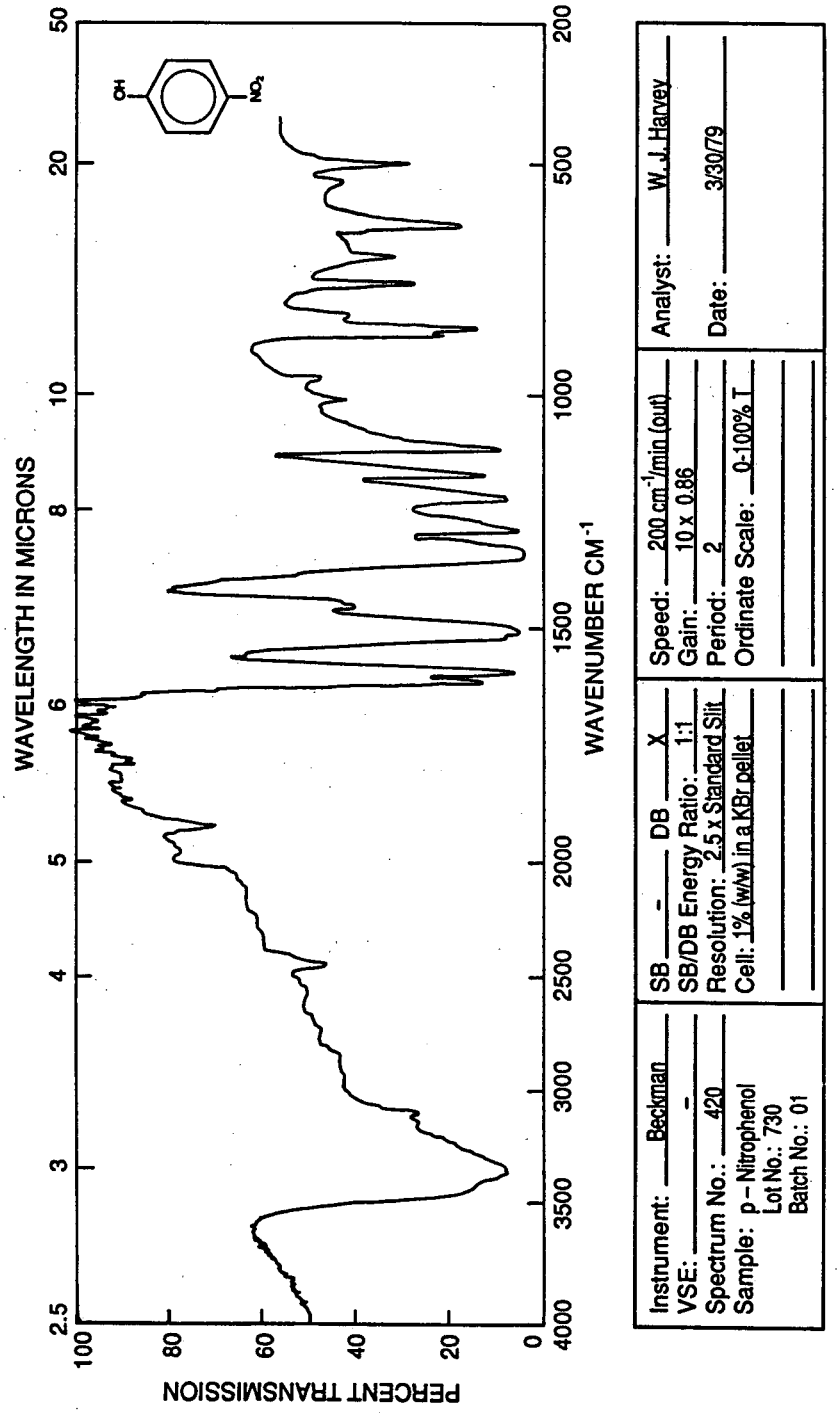


FIGURE E1
Infrared Absorption Spectrum of *p*-Nitrophenol

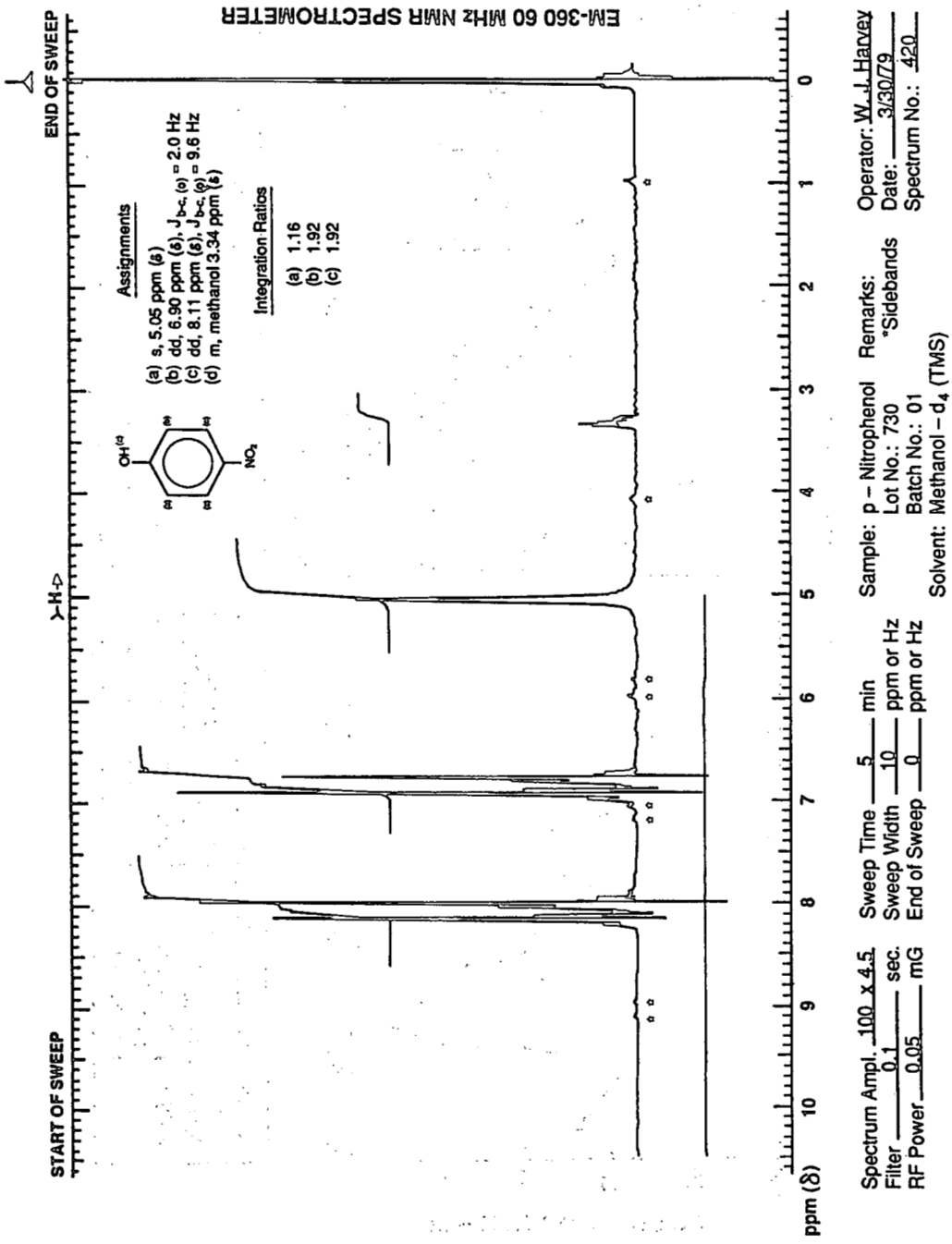


FIGURE E2
Nuclear Magnetic Resonance Spectrum of *p*-Nitrophenol

TABLE E1
Preparation and Storage of Dose Formulations in the 18-Month Dermal Studies of *p*-Nitrophenol

Preparation
p-Nitrophenol was dissolved in the appropriate amount of acetone (analytical reagent grade). Dose formulations were prepared every 2 weeks.

Initial Concentrations
0, 10, 20, and 40 mg/mL

Chemical Lot Number
p-Nitrophenol: 730
Acetone: 2440KVEZ

Maximum Storage Time
2 weeks

Storage Conditions
Stored at −20° C in amber glass vials with Teflon®-lined caps until the week of dosing, then at room temperature protected from light

TABLE E2
Results of Analysis of Dose Formulations for Mice in the 18-Month Dermal Studies of *p*-Nitrophenol

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
31 October 1984	2 November 1984	10	10.0	0
		20	21.0	+5
		40	40.8	+2
31 October 1984	13 November 1984[b]	10	10.1	+1
		20	21.1	+6
		40	40.9	+2
24 December 1984	28 December 1984	10.4	10.9	+5
		21.0	21.1	0
		41.6	43.6	+5
20 February 1985	21 February 1985	11.3	12.4	+10
		23.0	24.9	+8
		45.0	48.7	+8
17 April 1985	18 April 1985	12.32	13.4	+9
		24.96	26.4	+6
		49.20	50.3	+2
17 April 1985	1 May 1985[b]	12.32	13.3	+8
		24.96	26.2	+5
		49.20	53.1	+8
12 June 1985	13 June 1985	12.76	13.6	+7
		25.84	27.1	+5
		51.36	52.8	+3
7 August 1985	8 August 1985	12.96	13.7	+6
		26.32	27.8	+6
		51.84	54.0	+4
2 October 1985	3 October 1985	13.04	13.2	+1
		26.4	26.7	+1
		52.48	53.1	+1
2 October 1985	17 October 1985[b]	13.04	13.2	+1
		26.4	26.6	+1
		52.48	56.4	+7
4 December 1985	9 December 1985	13.36	13.9	+4
		27.36	28.6	+5
		53.76	55.4	+3
22 January 1986	28 January 1986	13.08	13.17	+1
		26.64	27.21	+2
		53.28	54.44	+2
19 March 1986	21 March 1986	13.64	13.74	+1
		27.76	28.25	+2
		54.72	55.90	+2
19 March 1986	4 April 1986[b]	13.64	14.80	+9
		27.76	30.59	+10
		54.72	58.27	+6

[a] Results of duplicate analyses
[b] Animal room sample

TABLE E3
Results of Referee Analysis of Dose Formulations for Mice in the 18-Month Dermal Studies of *p*-Nitrophenol

Date Mixed	Target Concentration	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
20 February 1985	11.3	12.4	11.9 ± 0.1
7 August 1985	51.84	54.0	52.7 ± 0.7
19 March 1986	27.76	28.3	27.8 ± 0.3

[a] Results of duplicate analyses
[b] Results of triplicate analyses

APPENDIX F
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE F1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE F2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE F3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.11 ± 0.52	21.1–23.1	18
Crude fat (% by weight)	5.69 ± 0.48	4.7–6.4	18
Crude fiber (% by weight)	3.37 ± 0.25	2.7–3.7	18
Ash (% by weight)	6.49 ± 0.24	6.1–7.0	18
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalanine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.098	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	9,522 ± 2,503	5,600–15,000	18
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α–Tocopherol (ppm)	37.95 ± 9.41	22.5–48.9	8
Thiamine (ppm)	20.33 ± 1.75	17.0–23.0	18
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.37	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 2.70	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 20.59	10.6–65.0	8
Choline (ppm)	3,089 ± 308	2,400–3,430	8
Minerals			
Calcium (%)	1.14 ± 0.10	0.95–1.41	18
Phosphorus (%)	0.92 ± 0.03	0.87–0.99	18
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	360.54 ± 100	255.0–523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.34	1.04–2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE F4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.74 ± 0.16	0.32–0.94	18
Cadmium (ppm)	<0.10		18
Lead (ppm)	0.55 ± 0.27	0.14–1.32	18
Mercury (ppm)	<0.05		18
Selenium (ppm)	0.33 ± 0.09	0.17–0.48	18
Aflatoxins (ppb)	<5.0		18
Nitrate nitrogen (ppm)	14.83 ± 3.97	2.80–19.0	18
Nitrite nitrogen (ppm)[b]	0.13 ± 0.10	<0.10–0.50	18
BHA (ppm)[c]	2.50 ± 0.98	<2.00–5.00	18
BHT (ppm)[c]	1.83 ± 1.04	<1.00–4.00	18
Aerobic plate count (CFU/g)[d]	43,065 ± 44,284	7,700–130,000	18
Coliform (MPN/g)[e,f]	19.89 ± 56.0	<3.00–240	18
	6.94 ± 9.63	<3.00–43.0	17
E. coli (MPN/g)[g]	3.06 ± 0.20	<3.00–4.0	18
Total nitrosamines (ppb)[h]	7.39 ± 3.66	3.80–16.0	18
N-Nitrosodimethylamine (ppb)[h]	6.18 ± 3.40	2.80–15.0	18
N-Nitrosopyrrolidine (ppb)[h]	1.22 ± 0.64	1.00–3.40	18
Pesticides (ppm)			
α-BHC[i]	<0.01		18
β-BHC	<0.02		18
γ-BHC	<0.01		18
δ-BHC	<0.01		18
Heptachlor	<0.01		18
Aldrin	<0.01		18
Heptachlor epoxide	<0.01		18
DDE	<0.01		18
DDD	<0.01		18
DDT	<0.01		18
HCB	<0.01		18
Mirex	<0.01		18
Methoxychlor	<0.05		18
Dieldrin	<0.01		18
Endrin	<0.01		18
Telodrin	<0.01		18
Chlordane	<0.05		18
Toxaphene	<0.1		18
Estimated PCBs	<0.2		18
Ronnel	<0.01		18
Ethion	<0.02		18
Trithion	<0.05		18
Diazinon	<0.1		18
Methyl parathion	<0.02		18
Ethyl parathion	<0.02		18
Malathion[j]	0.11 ± 0.16	0.05–0.69	18
Endosulfan I	<0.01		18
Endosulfan II	<0.01		18
Endosulfan sulfate	<0.03		18

TABLE F4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Two lots had values greater than 0.10 ppm. The lot milled 10 December 1984 measured 0.50 ppm and the lot milled 3 April 1986 measured 0.20 ppm.
[c] Source of contamination: soy oil and fish meal
[d] CFU = colony forming unit
[e] MPN = most probable number
[f] The mean, range, and standard deviation include one of high value of 240 CFU obtained in the lot milled 14 September 1984.
[g] One lot milled 14 September 1984 contained 4.0 MPN/g.
[h] All values were corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Seven lots contained more than 0.05 ppm.

APPENDIX G
SENTINEL ANIMAL PROGRAM

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF APRIL 1993

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF APRIL 1993 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3′-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4′-Diamino-2,2′-Stilbenedisulfonic Acid
413	Ethylene Glycol
415	Polysorbate 80
419	HC Hellow 4

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

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

Official Business
Penalty for Private Use - $300

NIH Publication No. 93-3148
April 1993