NTP TECHNICAL REPORT

ON THE

# TOXICOLOGY AND CARCINOGENESIS

# STUDIES OF *p*-NITROTOLUENE

(CAS NO. 99-99-0)

# IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

May 2002

NTP TR 498

NIH Publication No. 02-4432

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 and Prevention. 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. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP Reports printed since 1982 appears on the inside back cover.

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# CONTRIBUTORS

## National Toxicology Program

*Evaluated and interpreted results and reported findings*

J.K. Dunnick, Ph.D., Study Scientist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
L.T. Burka, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.A. Herbert, D.V.M., Ph.D.
J. Mahler, D.V.M.
R.R. Maronpot, D.V.M.
D.P. Orzech, M.S.
S.D. Peddada, Ph.D.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., ILS, Inc.

## Southern Research Institute

*Conducted studies and evaluated pathology findings*

C.D. Hébert, Ph.D., Study Director
J.D. Prejean, Ph.D., Principal Investigator
J.E. Heath, D.V.M.
D.R. Farnell, D.V.M., Ph.D.

## Experimental Pathology Laboratories, Inc.

*Provided pathology quality assurance*

J.F. Hardisty, D.V.M., Principal Investigator
G.E. Marrs, D.V.M., M.S.
C.C. Shackelford, D.V.M., M.S., Ph.D.

## Dynamac Corporation

*Prepared quality assurance audits*

S. Brecher, Ph.D., Principal Investigator

## Analytical Sciences, Inc.

*Provided statistical analyses*

R.W. Morris, M.S., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.
J.T. Scott, M.S.

## NTP Pathology Working Group

*Evaluated slides and prepared pathology report on rats (November 18, 1999)*

M.P. Jokinen, D.V.M., Chairperson
Pathology Associates, International
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J. Mahler, D.V.M.
National Toxicology Program
G.E. Marrs, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
G.A. Parker, D.V.M., Ph.D., Observer
ILS, Inc.
J.C. Seely, D.V.M.
PATHCO, Inc.
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

*Evaluated slides and prepared pathology report on mice (September 23, 1999)*

M.P. Jokinen, D.V.M., Chairperson
Pathology Associates, International
S. Ching, D.V.M., Ph.D.
SVC Associates
S. Hayashi, D.V.M., Ph.D.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J. Mahler, D.V.M.
National Toxicology Program
G.E. Marrs, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
A. Nyska, D.V.M.
National Toxicology Program

## Biotechnical Services, Inc.

*Prepared Technical Report*

S.R. Gunnels, M.A., Principal Investigator
M.P. Barker, B.A.
L.M. Harper, B.S.
E.S. Paal, M.S.J.
D.C. Serbus, Ph.D.

# CONTENTS

## Summary

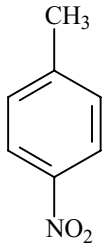
**Background:** Approximately 15 million pounds of *para*-nitrotoluene are used annually in the United States in the production of agricultural and rubber chemicals and dyes. We studied the effects of *p*-nitrotoluene on male and female rats and mice to identify potential toxic or carcinogenic hazards to humans.

**Methods:** We gave feed containing 1,250, 2,500, or 5,000 parts per million (ppm) *p*-nitrotoluene (equivalent to 0.125%, 0.25%, or 0.5%) to groups of 60 male and female rats and mice for 2 years. Groups of animals receiving untreated feed served as controls. Tissues from more than 40 sites were examined for every animal.

**Results:** All of the groups fed 5,000 ppm *p*-nitrotoluene weighed less than the controls. Significantly more clitoral gland tumors occurred in female rats receiving 2,500 ppm than in the control group. There were more subcutaneous fibromas and fibrosarcomas in male rats fed *p*-nitrotoluene and more lung tumors in male mice fed *p*-nitrotoluene than in the controls.

**Conclusions:** We conclude that the increased incidence of clitoral gland neoplasms in female rats was caused by exposure to *p*-nitrotoluene. Subcutaneous tumors in male rats and lung tumors in male mice may have been related to exposure to *p*-nitrotoluene.

# ABSTRACT



**_p_-NITROTOLUENE**

CAS No. 99-99-0

Chemical Formula: $C_7H_7NO_2$ Molecular Weight: 137.14

**Synonyms:** Methyl nitrobenzene; 1-methyl-4-nitrobenzene; 4-methylnitrobenzene; *p*-methylnitrobenzene; *p*-nitrophenylmethane; 4-nitrotoluol; 4-nitrotoluene; PNT

*p*-Nitrotoluene is used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper. *p*-Nitrotoluene was nominated by the National Institute for Occupational Safety and Health and the NTP for study based on its considerable human exposure as well as the absence of long-term studies of its carcinogenicity in rodents. Male and female F344/N rats and B6C3F$_1$ mice were exposed to *p*-nitrotoluene (greater than 99% pure) in feed for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, and rat and mouse bone marrow cells.

## 2-Year Study in Rats

Groups of 50 male and 50 female rats were fed diets containing 0, 1,250, 2,500, or 5,000 ppm *p*-nitrotoluene (equivalent to average daily doses of approximately 55, 110, or 240 mg *p*-nitrotoluene/kg body weight to males and 60, 125, or 265 mg/kg to females) for 105 or 106 weeks.

### *Survival, Body Weights, and Feed Consumption*

Survival of all exposed groups of rats was similar to that of the control groups. Mean body weights of 5,000 ppm male and 2,500 and 5,000 ppm female rats were less than those of the controls during most of the study; mean body weights of 1,250 ppm females were less during the second year of the study. Feed consumption by 5,000 ppm females was less than that by the controls during year 2 of the study.

### *Biomarkers of Exposure*

Two urinary metabolites were followed during the study as biomarkers of exposure. The ratios of *p*-nitrobenzoic acid to creatinine and of *p*-acetamidobenzoic acid to creatinine determined at 2 weeks and at 3, 12, and 18 months were linearly related to exposure concentration in males and females.

### *Pathology Findings*

The incidence of clitoral gland adenoma or carcinoma (combined) was significantly greater in 2,500 ppm

females than that in the controls and exceeded the historical control ranges. The incidence of clitoral gland neoplasms was not increased in 5,000 ppm females, possibly because of the lower body weights in this group. The incidences of subcutaneous fibroma and of subcutaneous fibroma or fibrosarcoma (combined) in 2,500 ppm male rats were significantly increased and exceeded the historical control ranges.

The incidences of several nonneoplastic kidney lesions were significantly increased in exposed groups of rats, and the severities of these lesions generally increased with increasing exposure concentration. In the spleen, incidences of hematopoietic cell proliferation and pigmentation were significantly increased in the 2,500 and 5,000 ppm groups. Significantly increased incidences of various types of altered cell foci in the liver of males and females were associated with exposure. Incidences of germinal epithelial atrophy of the testis in 5,000 ppm males and endometrial cystic hyperplasia of the uterus in 2,500 and 5,000 ppm females were significantly increased.

The incidences of mononuclear cell leukemia were significantly decreased in all exposed groups except 1,250 ppm females. The incidence of interstitial cell adenoma of the testis in 5,000 ppm males was significantly decreased.

## 2-Year Study in Mice

Groups of 50 male and 50 female mice were fed diets containing 0, 1,250, 2,500, or 5,000 ppm *p*-nitrotoluene (equivalent to average daily doses of approximately 170, 345, or 690 mg/kg to males and 155, 315, or 660 mg/kg to females) for 105 or 106 weeks.

### *Survival, Body Weights, and Feed Consumption*

Survival of all exposed groups of male and female mice was similar to that of the control groups. Mean body weights of 5,000 ppm males and females were less than those of the control groups during most of the study. Mean body weights of 2,500 ppm males were less than those of the controls after week 92. Feed consumption by all exposed groups of mice was similar to that by the control groups.

### *Pathology Findings*

The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was significantly greater in 5,000 ppm male mice than in the controls, as was the incidence of alveolar epithelial hyperplasia in this group. The incidences of alveolar epithelial bronchiolization were significantly increased in all exposed groups of males and females.

## Genetic Toxicology

*p*-Nitrotoluene was not mutagenic in any of several strains of *S. typhimurium*, with or without metabolic activation enzymes (S9). A positive response to *p*-nitrotoluene was observed in the L5178Y mouse lymphoma cell assay in trials with S9. Significantly increased sister chromatid exchange frequencies were observed in cultured Chinese hamster ovary cells treated with *p*-nitrotoluene with and without S9. Chromosomal aberrations were also induced in Chinese hamster ovary cells treated with *p*-nitrotoluene in the presence of S9; no increased aberrations were seen without S9. *p*-Nitrotoluene did not induce a significant reproducible increase in the frequency of micronuclei in bone marrow polychromatic erythrocytes of male rats or male mice when administered by intraperitoneal injection.

## Conclusions

Under the conditions of these 2-year feed studies there was *equivocal evidence of carcinogenic activity** of *p*-nitrotoluene in male F344/N rats based on increased incidences of subcutaneous skin neoplasms. There was *some evidence of carcinogenic activity* of *p*-nitrotoluene in female F344/N rats based on increased incidences of clitoral gland neoplasms. There was *equivocal evidence*

*of carcinogenic activity* of *p*-nitrotoluene in male $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *no evidence of carcinogenic activity* of *p*-nitrotoluene in female $B6C3F_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

Exposure to *p*-nitrotoluene caused increased incidences of nonneoplastic lesions of the kidney, spleen, and liver in male and female rats, testis in male rats, and lung in male and female mice.

Decreased incidences of mononuclear cell leukemia in male and female rats and testicular interstitial cell adenoma in male rats were attributed to exposure to *p*-nitrotoluene.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *p*-Nitrotoluene**

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Concentrations in feed** | 0, 1,250, 2,500, or 5,000 ppm | 0, 1,250, 2,500, or 5,000 ppm | 0, 1,250, 2,500, or 5,000 ppm | 0, 1,250, 2,500, or 5,000 ppm |
| **Body weights** | 5,000 ppm group less than the control group | Exposed groups less than the control group | 2,500 and 5,000 ppm groups less than the control group | 5,000 ppm group less than the control group |
| **Survival rates** | 31/50, 38/50, 38/50, 40/50 | 39/50, 37/50, 39/50, 41/50 | 46/50, 46/50, 45/50, 42/50 | 46/50, 47/50, 43/50, 49/50 |
| **Nonneoplastic effects** | Kidney: renal tubule hyaline droplet (2/50, 23/50, 27/50, 18/50); renal tubule pigmentation (10/50, 28/50, 47/50, 46/50)<br>Spleen: hematopoietic cell proliferation (9/50, 13/50, 19/50, 25/50); pigmentation (10/50, 12/50, 24/50, 38/50)<br>Liver: basophilic focus (31/50, 39/50, 42/50, 45/50); clear cell focus (20/50, 27/50, 30/50, 32/50); eosinophilic focus (5/50, 5/50, 5/50, 19/50)<br>Testis: germinal epithelial atrophy (7/50, 11/50, 8/50, 30/50) | Kidney: renal tubule hyaline droplet (8/50, 41/50, 49/50, 46/50); renal tubule pigmentation (9/50, 43/50, 49/50, 50/50); mineralization (15/50, 21/50, 32/50, 40/50); oncocytic renal tubule hyperplasia (0/50, 2/50, 4/50, 6/50)<br>Spleen: hematopoietic cell proliferation (26/50, 26/50, 45/50, 43/50); pigmentation (24/50, 32/50, 45/50, 48/50)<br>Liver: eosinophilic focus (1/50, 2/50, 7/50, 9/50) | Lung: alveolar epithelial bronchiolization (0/50, 20/50, 30/50, 48/50); alveolar epithelial hyperplasia (1/50, 1/50, 4/50, 6/50) | Lung: alveolar epithelial bronchiolization (0/50, 33/50, 41/50, 49/50) |
| **Neoplastic effects** | None | Clitoral gland: adenoma or carcinoma (8/50, 12/50, 20/50, 8/49) | None | None |
| **Equivocal findings** | Skin (subcutaneous): fibroma (1/50, 2/50, 7/50, 1/50); fibroma or fibrosarcoma (1/50, 2/50, 9/50, 1/50) | None | Lung: alveolar/ bronchiolar adenoma or carcinoma (8/50, 14/50, 12/50, 19/50) | None |

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *p*-Nitrotoluene**

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Decreased incidences** | Mononuclear cell leukemia: (24/50, 12/50, 5/50, 4/50)<br>Testis: interstitial cell adenoma (49/50, 46/50, 45/50, 34/50) | Mononuclear cell leukemia: (13/50, 12/50 3/50, 1/50) | None | None |
| **Level of evidence of carcinogenic activity** | Equivocal evidence | Some evidence | Equivocal evidence | No evidence |
| **Genetic toxicology** | | | | |
| *Salmonella typhimurium* gene mutations: | Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9 | | | |
| Mouse lymphoma gene mutations: | Positive with S9, negative without S9 | | | |
| Sister chromatid exchanges | | | | |
| Cultured Chinese hamster ovary cells *in vitro*: | Positive with and without S9 | | | |
| Chromosomal aberrations | | | | |
| Cultured Chinese hamster ovary cells *in vitro*: | Positive with S9, negative without S9 | | | |
| Micronucleated erythrocytes | | | | |
| Rat bone marrow *in vivo*: | Negative when administered by intraperitoneal injection | | | |
| Mouse bone marrow *in vivo*: | Negative when administered by intraperitoneal 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 cannot be evaluated because of major flaws **(inadequate study).** These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

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

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

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

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

## NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
## TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *p*-nitrotoluene on May 3, 2001 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

Stephen S. Hecht, Ph.D., Chairperson
University of Minnesota Cancer Centers
Minneapolis, MN

Linda A. Chatman, D.V.M.
Pfizer, Inc.
Groton, CT

Harold Davis, D.V.M., Ph.D., Principal Reviewer
Preclinical Safety Assessment
Amgen, Inc.
Thousand Oaks, CA

Yvonne P. Dragan, Ph.D.
School of Public Health
Ohio State University
Columbus, OH

Norman R. Drinkwater, Ph.D.
McArdle Laboratory for Cancer Research
University of Wisconsin-Madison
Madison, WI

James E. Klaunig, Ph.D., Principal Reviewer
Division of Toxicology
Department of Pharmacology and Toxicology
Indiana University/Purdue University at Indianapolis
Indianapolis, IN

David E. Malarkey, D.V.M., Ph.D.
Department of Microbiology, Pathology, and Parasitology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Michele Medinsky, Ph.D., Principal Reviewer*
Durham, NC

Walter W. Piegorsch, Ph.D.
Department of Statistics
University of South Carolina
Columbia, SC

Mary Anna Thrall, D.V.M.
Department of Pathology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, CO

---

* Did not attend

## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On May 3, 2001, the draft of the Technical Report on the toxicology and carcinogenesis studies of *p*-nitrotoluene received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of *p*-nitrotoluene 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 chemical-related neoplasms in male and female rats and mice. The proposed conclusions were *equivocal evidence of carcinogenic activity* in male F344/N rats, *some evidence of carcinogenic activity* in female F344/N rats, *equivocal evidence of carcinogenic activity* in male $B6C3F_1$ mice, and *no evidence of carcinogenic activity* in female $B6C3F_1$ mice.

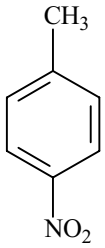
Dr. Davis, the first principal reviewer, questioned the use of the term uncertain findings to describe conclusions of equivocal evidence. He disagreed with the statement in the report that hematopoietic cell proliferation increased in the 5,000 ppm rats. Dr. Dunnick concurred. Dr. Davis also questioned whether there could be a relation between testicular interstitial cell adenomas and atrophy when the incidences of the former decreased while the latter increased. Dr. J. Mahler, NIEHS, explained that while atrophy can occur as a secondary effect of an adenoma, the absence of a neoplasm may increase the possibility of detecting a primary atrophic change. Dr. Davis also encouraged the inclusion of human exposure data whenever available.

Dr. Medinsky, the second principal reviewer, was unable to attend the meeting, and her comments were read into the record by Dr. M.S. Wolfe, NIEHS. Dr. Medinsky agreed with the proposed conclusions and focused on details of the discussion of metabolism and urinary biomarker data. Dr. Dunnick indicated that communications between NTP staff and Dr. Medinsky had resolved these questions.

Dr. Klaunig, the third principal reviewer, asked about the cause of apparent lower survival in control male rats compared with the high dose males. Dr. Dunnick noted that the survival in control male rats was normal for NTP studies, with mononuclear cell leukemia being one of the main causes of early deaths. However, in the exposed animals, splenic toxicity caused by the chemical inhibited the occurrence of mononuclear cell leukemia.

Dr. Davis moved that the conclusions be accepted as written and Dr. Klaunig seconded the motion, which was approved unanimously with eight votes.

# INTRODUCTION



***p*-NITROTOLUENE**

CAS No. 99-99-0

Chemical Formula: $C_7H_7NO_2$ Molecular Weight: 137.14

**Synonyms:** Methyl nitrobenzene; 1-methyl-4-nitrobenzene; 4-methylnitrobenzene; *p*-methylnitrobenzene; *p*-nitrophenylmethane; 4-nitrotoluol; 4-nitrotoluene; PNT

## CHEMICAL AND PHYSICAL PROPERTIES

The nitrotoluenes are produced by the nitration of toluene with an aqueous acidic mixture of sulfuric acid and nitric acid at a temperature that starts at 25° C and is slowly raised to 37° C. The resulting product contains 55% to 60% *o*-nitrotoluene, 3% to 4% *m*-nitrotoluene, and 35% to 40% *p*-nitrotoluene. The isomers may be separated by a combination of fractional distillation and crystallization (*Kirk-Othmer*, 1981). Isomers of nitrotoluene differ in the position of the nitro group in relation to the methyl group on the benzene ring. While the chemical formula is the same for all isomers, their chemical and physical properties vary (Table 1).

## PRODUCTION, USE, AND HUMAN EXPOSURE

*o*-Nitrotoluene and *p*-nitrotoluene are important commercial chemicals used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper. *p*-Nitrotoluene is on the United States Environmental Protection Agency's (1999) list of high production volume chemicals with an estimated production in 1990 of 18 million to 32 million pounds per year. In 1998, approximately 64,400 kg of *p*-nitrotoluene were imported to the United States (C. Robinson, U.S. International Trade Commission, personal communication).

Environmental surveys have detected *o*-nitrotoluene in rivers and drinking water (USEPA, 1976); all three isomers of nitrotoluene have been found in wastewater effluent and atmospheric emissions from industrial plants (Forsten, 1973; USEPA, 1976). Microbial systems are capable of biodegrading nitroaromatic compounds (Spain, 1995). The Occupational Safety and Health Administration set an 8-hour, time-weighted average (TWA) permissible exposure limit of 5 ppm (30 mg/m$^3$) for nitrotoluenes (NIOSH, 1997), and the American Conference of Governmental Industrial Hygienists (2000) recommended a threshold limit value of 2 ppm (11 mg/m$^3$) for the 8-hour TWA.

The National Occupational Exposure Survey (1981-1983) (NIOSH, 1990) found exposure to *p*-nitrotoluene

**TABLE 1**
**Chemical and Physical Properties of the Nitrotoluenes**[a]

| | *o*-Nitrotoluene | *m*-Nitrotoluene | *p*-Nitrotoluene |
|---|---|---|---|
| Boiling point | 220.4° C | 232.6° C | 238.3° C |
| Melting point | –9.3° C | 15° C | 51.7° C |
| Density (20° C) | 1.163 | 1.157 | 1.286 |
| Solubility ($H_2O$, 30° C) | 652 mg/L | 498 mg/L | 442 mg/L |
| Volatility (20° C) | 0.1 mm Hg | 0.1 mm Hg | 0.1 mm Hg |
| Volatility (30° C) | 0.25 mm Hg | 0.25 mm Hg | 0.25 mm Hg |
| Log octanol/water partition coefficient | 2.30 | 2.40 | 2.37 |

[a] Verschueren, 1983; NTP, 1992

among workers in five different occupational groups: biological technicians; painting and paint-spraying machine operators; machine operators; welders and cutters; and operators of separating, filtering, and clarifying machines. The last group accounted for approximately 60% of potential exposures. An estimated 4,350 people in the United States are potentially exposed to *p*-nitrotoluene in the workplace annually. Data on exposure potential in the workplace for the *ortho* and *meta* isomers were not available.

## ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

### *Experimental Animals*

The comparative metabolism of *o*-, *m*-, and *p*-nitrotoluene administered orally was studied in F344 rats (Chism *et al*., 1984, deBethizy and Rickert, 1984; Chism and Rickert, 1985; Rickert *et al*., 1987). Following an oral dose of the three radiolabeled compounds as individual chemicals, 73% to 86% of the dose was excreted in the urine within 72 hours. Fecal excretion accounted for 5% to 13% of the dose, and minimal amounts of radiolabel were captured in expired breath (Chism *et al*., 1984).

Metabolism studies (Appendix K) were designed to compare the *in vivo* metabolism of *p*-nitrotoluene in F344/N rats and $B6C3F_1$ mice and to determine the effects of dose and of repeated dosing on rates and routes of excretion. The routes of excretion were similar in rats and mice, with the predominant route being via urine. The slightly higher amount of [$^{14}$C]-*p*-nitrotoluene-derived radioactivity in feces of mice can be attributed to contamination of the feces by urine. The rate of excretion was similar in rats and mice with at least 70% of the administered radioactivity excreted in urine in the first 24 hours.

There is good agreement between the current comparative metabolism studies (Appendix K) and those reported by Chism *et al*. (1984) on the major urinary metabolites in male rats. The urinary metabolite profile after nine daily doses of 200 mg *p*-nitrotoluene/kg body weight appeared similar to that seen after a single dose. There were striking differences between the urinary metabolite profiles of rats and mice (Appendix K). Ring-hydroxylation was a major metabolic pathway in mice but a very minor one in rats. The extent of ring-hydroxylation appeared to be dose-related; there was relatively more methyl group oxidation and nitro-group reduction after administration of 200 mg/kg than after administration of 2 mg/kg. *p*-Nitrobenzylmercapturic acid was found only in rats. The presence of this mercapturic acid indicates that a potentially reactive benzylating agent is formed during metabolism of *p*-nitrotoluene in rats. The major urinary metabolites of

**TABLE 2**
**Urinary Metabolites of *o*-, *m*-, and *p*-Nitrotoluene in Male Rats and Mice Administered Gavage Doses of 200 mg/kg[a]**

| | *o*-Nitrotoluene | *m*-Nitrotoluene | *p*-Nitrotoluene |
|---|---|---|---|
| **Rats**[b] | | | |
| | *o*-Nitrobenzoic acid (29%) | *m*-Nitrobenzoic acid (21%) | *p*-Nitrobenzoic acid (28%) |
| | *o*-Nitrobenzyl glucuronide (14%) | *m*-Nitrohippuric acid (24%) | *p*-Nitrohippuric acid (13%) |
| | S-(*o*-Nitrobenzyl)-N-acetylcysteine (12%) | *m*-Acetamidobenzoic acid (12%) | *p*-Acetamidobenzoic acid (27%) |
| **Mice**[c] | | | |
| | *o*-Nitrobenzoic acid (38%) | *m*-Nitrohippuric acid (52%) | *p*-Nitrohippuric acid (20%) |
| | *o*-Nitrobenzyl glucuronide (24%) | *m*-Nitrobenzoic acid (19%) | 2-Methyl-5-nitrophenyl glucuronide (13%) |
| | | | 2-Methyl-5-nitrophenyl sulfate (19%) |

[a] Percentage of administered dose
[b] Chism *et al.*, 1984
[c] Appendix K; RTI, 1995, 1996a,b

the three nitrotoluene isomers that have been identified in rats and mice are shown in Table 2. A detailed metabolic scheme for *p*-nitrotoluene is shown in Figure 1.

All three isomers apparently are converted to the corresponding benzyl alcohol and to benzoic acid (Table 2); the *meta* and *para* isomers undergo conjugation with glycine to form the hippuric acid, or nitro reduction and acylation. For *o*-nitrotoluene, formation of *o*-nitrobenzyl alcohol glucuronide is a major metabolic pathway. Conjugation with glucuronic acid is not a major metabolic route for the *meta* and *para* isomers. The *o*-nitrobenzyl glucuronide is excreted via the bile into the intestine, where bacterial enzymes reduce the nitro group to form aminobenzyl alcohol. The aminobenzyl alcohol is reabsorbed and further metabolized by hepatic enzymes to a species capable of covalent binding to hepatic DNA. Studies by Chism and Rickert (1985) suggested that *o*-aminobenzyl sulfate is the metabolite of *o*-nitrotoluene responsible for binding covalently to DNA.

An analogous metabolic pathway is followed by 2,6-dinitrotoluene (2,6-DNT), which is oxidized in the liver to 2,6-dinitrobenzyl alcohol, then conjugated with glucuronic acid and excreted in the bile (Kedderis *et al*., 1984). Intestinal microflora hydrolyze the glucuronide and reduce the nitro group to form 2-amino-6-nitrobenzyl alcohol. A portion of this metabolite is reabsorbed from the intestine and oxidized to a hydroxylamine by hepatic enzymes. The hydroxylamine is then conjugated with sulfate by hepatic sulfotransferase. The unstable N,O-sulfate decomposes to form an electrophilic nitrenium ion that can react with cellular nucleophiles such as DNA. This electrophilic ion is formed in the liver, hence the high carcinogenic activity of 2,6-DNT for rodent liver 2,6-DNT is more active than 2,4-DNT in an *in vivo/in vitr*o hepatocyte unscheduled DNA synthesis assay (Mirsalis and Butterworth, 1982).

The metabolic profiles for 2,6-DNT and *o*-nitrotoluene are similar (Rickert *et al*., 1987). Both are excreted as glucuronides into the intestine where bacterial enzymes reduce the nitro groups; the aminobenzyl alcohols are reabsorbed and further metabolized in the liver to electrophilic compounds which presumably can interact with DNA. Binding of 2,6-DNT and *o*-nitrotoluene to rat hepatic DNA is decreased by pretreatment with sulfotransferase inhibitors, suggesting that the final step in the activation of each chemical is formation of an unstable N,O-sulfate that decomposes to yield an electrophilic nitrenium ion.

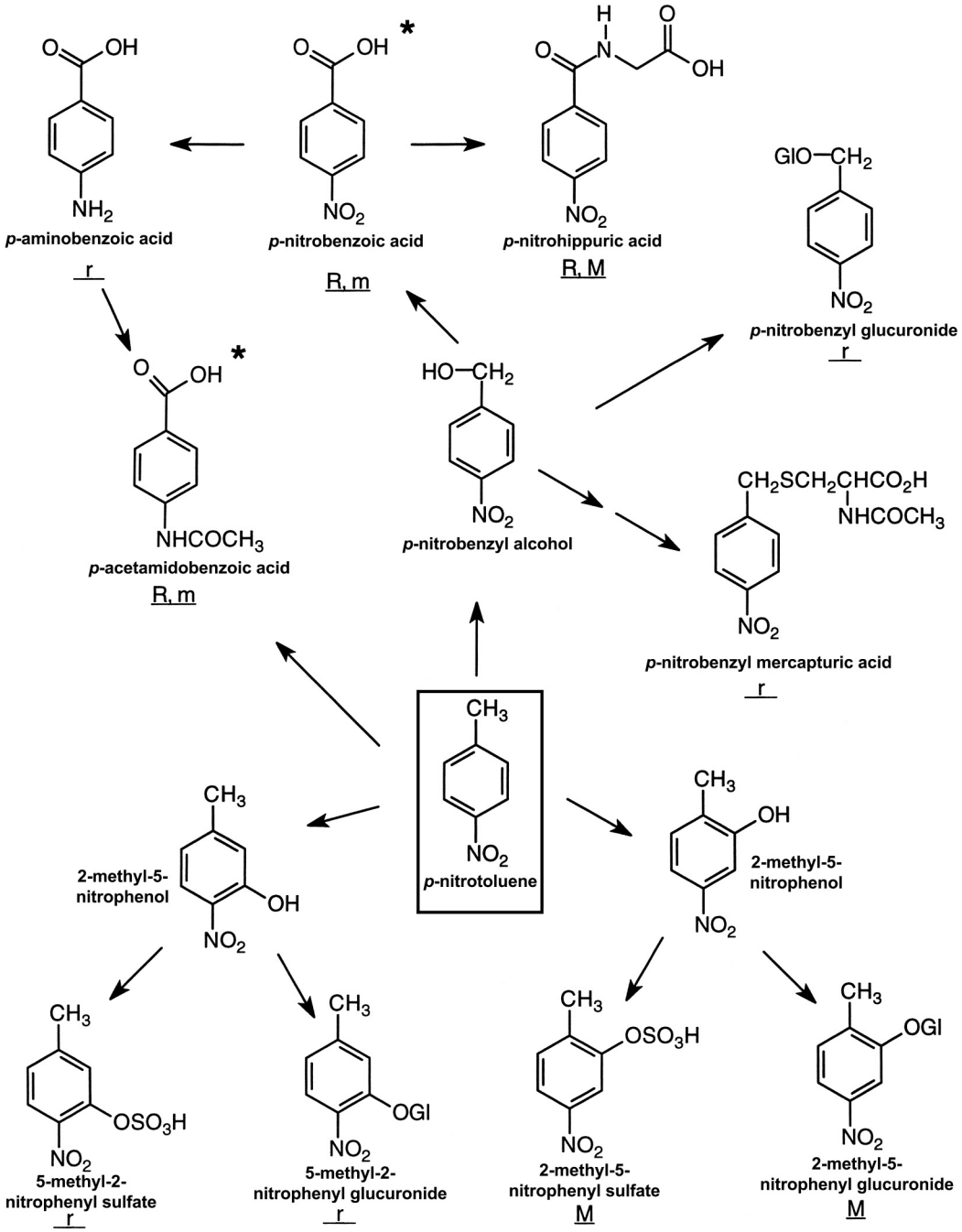



**FIGURE 1**
**Composite Metabolic Scheme for *p*-Nitrotoluene in Rats and Mice** (Chism *et al.*, 1984; Appendix K)
Abbreviations: Major (R) or minor (r) urinary metabolite in rats; major (M) or minor (m) urinary metabolite in mice. *Measured in urine in NTP studies

### *Humans*

No information on the absorption, distribution, metabolism, or excretion of *o*-, *m*-, or *p*-nitrotoluene in humans was found in a review of the available literature.

## TOXICITY

### *Experimental Animals*

Oral $LD_{50}$ values are 2,144 mg/kg (rats) and 1,231 mg/kg (mice) for *p*-nitrotoluene, 891 mg/kg (rats) and 2,463 mg/kg (mice) for *o*-nitrotoluene, and 1,072 mg/kg (rats) and 330 mg/kg (mice) for *m*-nitrotoluene. These acute toxicity studies did not include histopathologic examination of tissues (Ciss *et al*., 1980a,b).

In 14-day studies (NTP, 1992), *o*-, *m*-, or *p*-nitrotoluene was administered in feed to male and female F344/N rats and $B6C3F_1$ mice at concentrations ranging from 388 to 20,000 ppm (equivalent to average daily doses of 55 to 900 mg nitrotoluene/kg body weight). There were no effects on survival or clinical findings of toxicity in these studies, although animals at the higher exposure concentrations showed decreases in body weight gains relative to controls.

In 13-week studies (NTP, 1992), *o*-, *m*-, and *p*-nitrotoluene were each given to male and female F344/N rats and $B6C3F_1$ mice in feed at concentrations from 625 to 10,000 ppm. The estimated daily doses based on measures of feed consumption were similar for each of the three isomers and ranged from 40 to 725 mg nitrotoluene/kg body weight per day for rats and 45 to 680 mg/kg per day for mice. There were no effects on survival, and clinical findings of toxicity were limited to decreases in feed consumption. Decreased body weight gains occurred in exposed rats and mice at the higher exposure concentrations and were most pronounced in rats receiving *o*-nitrotoluene.

In the 13-week NTP (1992) studies, toxicity to the kidney, spleen, and testis occurred in rats receiving any of the three isomers, and toxicity to the liver and mesothelium occurred in male rats given *o*-nitrotoluene (Table 3). Kidney toxicity in male rats was characterized by the presence of hyaline droplets in tubule epithelial cells, attributed to an increase in the level of $\alpha$2u-globulin (as determined by ELISA). No granular casts were seen, and this was considered to be only minimal toxicity to the kidney. Pigment, possibly lipofuscin, and karyomegaly were present in the renal tubule epithelium of exposed male and female rats in the *p*-nitrotoluene study (Table 4). In the spleen of exposed male and female rats, there were mild increases in the incidences of hematopoiesis, hemosiderin deposition, and/or congestion; this effect was most severe with the *para* isomer, followed by the *ortho* and then the *meta* isomer. Administration of *o*-, *m*-, or *p*-nitrotoluene impaired testicular function of the rat, as shown by degeneration of the testis and reduction in sperm concentration, motility, and spermatid number. All three isomers increased the length of the estrous cycle in rats. Hepatic toxicity was characterized by cytoplasmic vacuolization, oval cell hyperplasia, an increase in the concentration of serum bile acids, and increased sorbitol dehydrogenase and alanine aminotransferase activities in male rats given *o*-nitrotoluene. There was no histopathologic evidence for liver toxicity in male or female rats with the *meta* or *para* isomers, or in female rats with the *ortho* isomer, but evidence of liver injury was observed in these groups as indicated by increased relative liver weights and elevated bile acids and liver enzymes in serum. Mesotheliomas of the tunica vaginalis were observed in 3 of 10 male rats receiving 5,000 ppm *o*-nitrotoluene, and mesothelial cell hyperplasia was observed in 2 of 10 male rats receiving *o*-nitrotoluene at 10,000 ppm.

The only histopathologic evidence for toxicity in mice in the 13-week studies (NTP, 1992) occurred in animals receiving *o*-nitrotoluene, which caused degeneration and metaplasia of the olfactory epithelium. No liver lesions were noted in mice, but the three isomers caused increases in relative liver weights. There was no toxicity to the reproductive system in male or female mice treated with any of the nitrotoluene isomers.

Immunotoxicity was evaluated in female $B6C3F_1$ mice receiving *p*-nitrotoluene by gavage at doses of 200, 400, or 600 mg/kg for 14 days (Burns *et al.*, 1994). The livers of 400 and 600 mg/kg mice showed mild swelling of hepatocytes but no evidence of necrosis. The proportion of monocytes in blood was decreased in mice treated with *p*-nitrotoluene. Various immunologic endpoints were measured after the 14-day dosing period. *p*-Nitrotoluene suppressed the IgM response to sheep red blood cells and the delayed hypersensitivity response to a sample antigen (Keyhole limpet hemocyanin). There was a 24% decrease in the percentage of $CD4^+$

**TABLE 3**
**Summary of Selected Treatment-Related Effects in the 13-Week Nitrotoluene Feed Studies**[a]

| | *o*-Nitrotoluene | | *m*-Nitrotoluene | | *p*-Nitrotoluene | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| **Rats** | | | | | | |
| Final mean body weight (90% or less of controls) | 2,500 | 2,500 | 10,000 | 10,000 | 5,000 | 10,000 |
| Changes in hematology parameters | 2,500 | 2,500 | 5,000 | 5,000 | 2,500 | 2,500 |
| Liver | | | | | | |
| Increased relative weight | 625 | 625 | 10,000 | 10,000 | 5,000 | 10,000 |
| Increased ALT | 5,000 | —[b] | — | 5,000 | — | 10,000 |
| Increased SDH | 2,500 | — | — | — | — | — |
| Increased bile acids | 5,000 | 10,000 | 5,000 | 10,000 | 10,000 | — |
| Nonneoplastic lesions | 2,500 | — | — | — | — | — |
| Kidney | | | | | | |
| Increased relative weight | 2,500 | 1,250 | 10,000 | 5,000 | 5,000 | 10,000 |
| Nonneoplastic lesions | 1,250 | 2,500 | 625 | — | 625 | 625 |
| Spleen | | | | | | |
| Nonneoplastic lesions | 1,250 | 2,500 | 2,500 | 2,500 | 625 | 625 |
| Testis | | | | | | |
| Decreased spermatid count | 5,000 | | 10,000 | | 10,000 | |
| Nonneoplastic lesions | 5,000 | | 10,000 | | 10,000 | |
| Epididymal mesothelium | | | | | | |
| Neoplastic and preneoplastic lesions | 5,000 | | — | | — | |
| Increased estrous cycle length | | 10,000 | | 5,000 | | 10,000 |
| **Mice** | | | | | | |
| Final mean body weight (90% or less of control) | 2,500 | 2,500 | 10,000 | 10,000 | 10,000 | 10,000 |
| Nose | | | | | | |
| Nonneoplastic lesions | 1,250 | 1,250 | — | — | — | — |
| Liver | | | | | | |
| Increased relative weight | 2,500 | 1,250 | 625 | 625 | 625 | 625 |

[a] NTP, 1992; lowest exposure group (ppm) in which a chemical-related effect was seen; ALT=alanine aminotransferase; SDH=sorbitol dehydrogenase

[b] Not observed in any exposure group

**TABLE 4**
**Treatment-Related Lesions in F344/N Rats in the 13-Week Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 625 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm | 10,000 ppm |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Kidney[b] | 10 | 10 | 10 | 10 | 10 | 10 |
| Nephropathy, Hyaline Droplet[c] | 0 | 10** (1.0)[d] | 10** (1.0) | 10** (1.0) | 10** (2.0) | 10** (2.0) |
| Karyomegaly | 0 | 0 | 3 (1.0) | 5* (1.0) | 10** (2.0) | 10** (2.0) |
| Pigmentation | 0 | 0 | 0 | 0 | 0 | 10** (1.0) |
| Spleen | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematopoiesis | 0 | 6** (1.0) | 9** (1.0) | 10** (1.1) | 10** (1.2) | 10** (2.2) |
| Pigmentation | 0 | 6** (1.0) | 8** (1.0) | 10** (1.1) | 9** (1.3) | 10** (2.4) |
| Congestion | 0 | 8** (1.0) | 10** (1.0) | 9** (1.0) | 10** (1.0) | 10** (2.0) |
| Testis | 10 | 10 | 10 | 10 | 10 | 10 |
| Seminiferous Tubule Degeneration | 0 | 0 | 1 (2.0) | 0 | 1 (2.0) | 4* (1.8) |
| **Female** | | | | | | |
| Kidney | 10 | 10 | 10 | 10 | 10 | 10 |
| Karyomegaly | 0 | 10** (1.0) | 10** (1.0) | 10** (2.0) | 10** (2.0) | 10** (2.0) |
| Pigmentation | 0 | 10** (1.0) | 10** (1.0) | 10** (1.0) | 10** (2.0) | 10** (2.0) |
| Spleen | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematopoiesis | 0 | 4* (1.0) | 4* (1.7) | 5* (1.2) | 9** (1.2) | 10** (1.8) |
| Pigmentation | 0 | 5* (1.0) | 6** (1.0) | 10** (1.6) | 10** (1.9) | 10** (2.0) |
| Congestion | 0 | 4* (1.0) | 6** (1.0) | 10** (1.0) | 10** (1.2) | 10** (2.0) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Data presented by Dunnick *et al.* (1994)
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

T lymphocytes in the spleen. There was no dose-dependent alteration of peritoneal macrophage numbers or differential counts, unstimulated natural killer cell activity, response to B cell mitogen LPS, C3 activity, or interferon levels. Exposure of mice to *p*-nitrotoluene decreased resistance to *Listeria monocytogenes* but not to *Streptococcus pneumoniae*. The decreased host resistance to *L. monocytogenes* can be attributed to the decrease in T lymphocytes and to a decreased delayed hypersensitivity response. The authors concluded that the immune system is an important target for toxicity of *p*-nitrotoluene and that the T cell is the most sensitive cell to *p*-nitrotoluene toxicity. The immunological dysfunction seen after *p*-nitrotoluene exposure was related to chemical-induced toxicity to the T helper function (Burns *et al.*, 1994).

### *Humans*

No epidemiology studies or reports of health effects related to exposure to *o*-, *m*-, or *p*-nitrotoluene were found in a review of the literature.

## CARCINOGENICITY

### *Experimental Animals*

Interest in the carcinogenicity of mononitrotoluenes stems from the results of long-term rodent studies using technical-grade DNT, 2,6-DNT, or 2,4-DNT. Results of these studies suggest that 2,6-DNT is a potent carcinogen in rat liver (Rickert *et al*., 1984). The results of Weisburger *et al*. (1978) also suggested *ortho*-substituted aromatic compounds are more potent carcinogens than corresponding isomers with *meta* or *para*

substitutions. This was seen with *o*-, *m*-, and *p*-toluidine in rats and mice, as well as with other compounds. The toluidine studies are of interest because reduction of the nitro group of the nitrotoluenes yields the corresponding toluidine. The National Cancer Institute (1979) reported that *o*-toluidine hydrochloride was carcinogenic in 2-year studies in male rats (mesotheliomas, splenic sarcomas, subcutaneous fibromas), in female rats (splenic sarcomas, urinary bladder transitional cell tumors, tumors of the mammary gland), in male mice (hemangioma, hemangiosarcoma), and in female mice (liver tumors).

### *Humans*

No epidemiological studies of *o*-, *m*-, or *p*-nitrotoluene were found in a review of the literature.

## Genetic Toxicity

Testing of the mononitrotoluenes *in vitro* for mutagenicity has generally yielded negative results, although occasional positive responses in various assays have been reported. A recent review of the mutagenicity data for the mononitrotoluenes was provided by the International Agency for Research on Cancer (1996). The aromatic nitro group of the nitrotoluenes is considered a structural alert to potential DNA reactivity (Tennant and Ashby, 1991), but such activity would presumably be dependent upon the metabolic capability of the test system. For example, reduction of the nitro group to produce an aromatic amine would likely be necessary for a positive response in the *Salmonella typhimurium* assay. Although *o*- and *m*-nitrotoluene demonstrated no mutagenic activity in any of several strains of *S. typhimurium*, with or without S9 metabolic activation, isolated positive responses were reported for *p*-nitrotoluene in strain TA100, with and without S9 (Chiu *et al*., 1978; Miyata *et al*., 1981; Spanggord *et al*., 1982; Haworth *et al*., 1983; Suzuki *et al*., 1983; Shimizu and Yano, 1986; Kawai *et al*., 1987). *p*-Nitrotoluene also induced cell growth inhibition, a measure of DNA damage, in *Bacillus subtilis* M45/H17 in the absence of S9 (Shimizu and Yano, 1986); *o*-nitrotoluene was weakly positive in this assay and results with *m*-nitrotoluene were negative.

All three mononitrotoluene isomers induced sister chromatid exchanges in cultured Chinese hamster ovary (CHO) cells; only *m*-nitrotoluene required S9 for a positive response (Galloway *et al.*, 1987). *p*-Nitrotoluene induced chromosomal aberrations in cultured CHO cells in the presence of S9 (Galloway *et al.*, 1987), but no increases in the frequency of micronuclei or chromosomal aberrations were observed in bone marrow cells of male B6C3$F_1$ mice administered *p*-nitrotoluene as a single intraperitoneal injection (Furukawa *et al.*, 1989; Ohuchida *et al.*, 1989).

No induction of unscheduled DNA synthesis was observed in male F344 rat hepatocytes or spermatocytes treated with *m*- or *p*-nitrotoluene in the standard *in vitro* assay (Doolittle *et al.*, 1983; Working and Butterworth, 1984) or *in vivo* (Doolittle *et al.* 1983; Butterworth *et al.*, 1989; Mirsalis *et al.*, 1989). Positive results were obtained, however, in an *in vitro* unscheduled DNA synthesis assay employing serum-free medium (Parton *et al.*, 1995). *o*-Nitrotoluene was also negative in the *in vitro* unscheduled DNA synthesis assay, but in male F344 rats treated *in vivo*, a strongly positive response was observed (Doolittle *et al.*, 1983). No induction of unscheduled DNA synthesis by *o*-nitrotoluene was noted in germ-free male rats, indicating that activation of *o*-nitrotoluene, or an intermediate metabolic conjugate, by intestinal bacteria is necessary to the process. No induction of unscheduled DNA synthesis was observed in hepatocytes of female rats treated with *o*-nitrotoluene *in vivo*; differences in *in vivo* results between the sexes may be due to differences in hepatic metabolism or disposition of *o*-nitrotoluene. Different results between males and females have been attributed to males excreting more of the glucuronide conjugates of the nitrotoluenes into the bile and, subsequently, into the intestine where they are metabolized further by bacterial systems. Gender-related differences in metabolism have also been observed with the dinitrotoluenes in rats (Rickert and Long, 1980, 1981).

Covalent binding to hepatic macromolecules and to DNA was measured in hepatocytes of male F344 rats after a single oral dose of *o*-, *m*-, or *p*-nitrotoluene (Rickert *et al.,* 1987). Only *o*-nitrotoluene bound DNA, whereas all three isomers bound protein.

## Study Rationale

The National Institute for Occupational Safety and Health and the NTP nominated the nitrotoluenes for rodent toxicity and carcinogenicity studies based on the considerable human exposure to these chemicals as well as the lack of long-term studies of carcinogenicity in

rodents. This Technical Report describes the results of the 2-year studies of *p*-nitrotoluene in F344/N rats and $B6C3F_1$ mice. The 2-year studies of *o*-nitrotoluene are reported in a companion Technical Report (NTP, 2002).

The exposure concentrations for the 2-year studies of *p*-nitrotoluene (0, 1,250, 2,500 and 5,000 ppm) were selected based on the findings from the 13-week studies (NTP, 1992). In those studies, body weights of 10,000 ppm rats and mice were 11% to 28% lower than those of controls. Toxicity at 5,000 ppm was considered to be minimal. Based on these findings, the exposure concentrations selected for the 2-year rat and mouse studies were 0, 1,250, 2,500, and 5,000 ppm.

# MATERIALS AND METHODS

## PROCUREMENT AND CHARACTERIZATION OF *p*-NITROTOLUENE

*p*-Nitrotoluene was obtained from SAF Bulk Chemicals (St. Louis, MO) in one lot (338297/1495). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and the study laboratory (Appendix G). Reports on analyses performed in support of the *p*-nitrotoluene studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, pale yellow, crystalline solid, was identified as *p*-nitrotoluene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and low- and high-resolution mass spectrometry. The purity was determined by Karl Fischer water analysis and gas chromatography. Karl Fischer water analysis indicated 0.694% water. Gas chromatography by three systems indicated one major peak and one impurity with an area less than 0.3% relative to the major peak. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by Midwest Research Institute (Kansas City, MO) using gas chromatography. No degradation of the bulk chemical was observed after storage for 2 weeks, protected from light, at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at approximately 5° C in sealed containers. Stability was monitored during the 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

## PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 2 weeks by mixing *p*-nitrotoluene with feed (Table G2). Stability studies of the 1,250 ppm dose formulation and homogeneity studies of the 1,250 and 5,000 ppm dose formulations in nonirradiated NTP-2000 feed were performed by the analytical chemistry laboratory using gas chromatography. Homogeneity studies of the 1,250 and 5,000 ppm dose formulations in nonirradiated NTP-2000 feed and the 1,250, 2,500, and 5,000 ppm blends in irradiated feed were performed by the study laboratory using gas chromatography. Stability of the dose formulations was confirmed for 35 days when stored in the dark at temperatures up to 3° C; significant chemical losses due to volatility were seen in the dose formulations under simulated animal room conditions. Homogeneity was confirmed in each study.

Periodic analyses of the dose formulations of *p*-nitrotoluene were conducted by the study laboratory every 8 to 12 weeks using gas chromatography (Table G3). Of the dose formulations analyzed and used, all 248 had concentrations that were between 90% to 115% of the target concentration. Because of the expected losses from volatility during formulation, dose formulations were prepared at up to 115% of the target concentrations.

## 2-YEAR STUDIES

### Study Design

Groups of 50 male and 50 female rats and mice were fed diets containing 0, 1,250, 2,500, or 5,000 ppm *p*-nitrotoluene for 105 or 106 weeks. The exposure concentrations were selected based on the results of earlier studies (NTP, 1992) in which rats and mice received up to 10,000 ppm *p*-nitrotoluene in feed for 13 weeks; in those studies, reduced body weight gains were seen at concentrations greater than 5,000 ppm.

### Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. The animals were quarantined for 12 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 5 to 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

## Animal Maintenance

Rats were housed two or three (males) or five (females) per cage; male mice were housed individually and female mice were housed five per cage. Feed and water were available *ad libitum*. Feed consumption was measured for a 1-week period every 4 weeks. The estimate of dose delivered to the animals (mg/kg) was based on body weight and feed consumption data collected during the course of the 2-year studies and targeted chemical concentration in the feed. Animals were given nonirradiated feed from the beginning of the studies until July 22, 1996, and irradiated feed from then until the end of the studies. The feed was irradiated to reduce potential microbial contamination. Cages and racks were rotated approximately every 2 weeks. Dose formulations were replaced in animal room feeders on a 2-day, 2-day, 3-day schedule, due to the formulations' instability under animal room conditions. Further details of animal maintenance are given in Table 5. Information on feed composition and contaminants is provided in Appendix I.

## Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded every 4 weeks. Animals were weighed initially, during week 4, and every 4 weeks thereafter.

Five male and five female rats from each group were randomly selected for urinalysis at 2 weeks and 3, 12, and 18 months. Animals were placed in metabolism cages for 24 hours. Urine samples were placed on ice, urine volume and creatinine were measured, and then the samples were frozen pending metabolite analysis.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of approximately 5 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 5.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For these studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included liver, kidney, spleen, testis, uterus, and mammary gland (females only) of rats and the lung, liver, and thyroid gland of mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of exposure groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

## Urinary Metabolite Analyses

To establish the correlation between exposure concentration and internal dose and to determine how metabolism of *p*-nitrotoluene may change with chronic exposure and age, two urinary metabolites were chosen as biomarkers based on the metabolism studies of Chism *et al*. (1984). *p*-Acetamidobenzoic acid was chosen as a representative of the nitro-reduction pathway. *p*-Nitrobenzoic acid was chosen as a representative of the methyl-oxidation pathway. Metabolite concentrations were determined by high-performance liquid chromatography (HPLC). An internal standard solution of benzoic acid in water and

sodium hydroxide was added to the urine samples, which were then diluted with a mobile phase of methanol in potassium phosphate buffer. Phosphoric acid was used to adjust the pH to 2.6 to 2.7, and the resulting mixture was filtered and degassed by sonication. The samples were then analyzed by HPLC using a C-18 column with ultraviolet detection (266 nm). The ratios obtained by dividing the metabolite concentration by the creatinine concentration, rather than the mass of metabolite excreted per 24 hours, were analyzed.

**TABLE 5**
**Experimental Design and Materials and Methods in the 2-Year Feed Studies of *p*-Nitrotoluene**

**Study Laboratory**
Southern Research Institute (Birmingham, AL)

**Strain and Species**
F344/N rats
B6C3F$_1$ mice

**Animal Source**
Taconic Laboratory Animals and Services (Germantown, NY)

**Time Held Before Studies**
12 days

**Average Age When Studies Began**
5 to 6 weeks

**Date of First Exposure**
Rats: November 28, 1995
Mice: November 14, 1995

**Duration of Exposure**
105 to 106 weeks

**Date of Last Exposure**
Rats: November 25-December 3, 1997
Mice: November 11-18, 1997

**Average Age at Necropsy**
110 to 111 weeks

**Size of Study Groups**
50 males and 50 females

**Method of Distribution**
Animals were distributed randomly into groups of approximately equal initial mean body weights.

**Animals per Cage**
Rats: 2 or 3 (males) or 5 (females)
Mice: 1 (males) or 5 (females)

**Method of Animal Identification**
Tail tattoo

**Diet**
NTP-2000 Open Formula Meal (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*. Animals received nonirradiated feed from the beginning of the studies through July 22, 1996, and irradiated feed from July 22, 1996, to the end of the studies.

**Water**
Tap water (Birmingham municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI) available *ad libitum*

**Cages**
Polycarbonate (Lab Products, Inc., Maywood, NJ) changed at least twice a week (rats and female mice) or once weekly (male mice)

**Bedding**
Heat-treated hardwood bedding chips (P.J. Murphy Forest Products, Inc., Montville, NJ)

**Cage Filters**
Reemay® spun-bonded polyester (Andico, Birmingham, AL), changed every 2 weeks

**TABLE 5**
**Experimental Design and Materials and Methods in the 2-Year Feed Studies of *p*-Nitrotoluene**

**Racks**
Stainless steel, changed every 2 weeks

**Animal Room Environment**
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

**Exposure Concentrations**
0, 1,250, 2,500, and 5,000 ppm in feed, available *ad libitum*

**Type and Frequency of Observation**
Observed twice daily; animals were weighed initially, during week 4, and every 4 weeks thereafter; clinical findings were recorded at 4-week intervals. Feed consumption was measured over a 1-week period every 4 weeks.

**Method of Sacrifice**
Carbon dioxide asphyxiation

**Necropsy**
Necropsies were performed on all animals.

**Urinalysis**
Urine was collected during a 24-hour period from five male and five female rats and mice from each group at 2 weeks and 3, 12, and 18 months. Parameters evaluated included urine volume, creatinine, *p*-acetamidobenzoic acid and *p*-nitrobenzoic acid.

**Histopathology**
Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone, brain, clitoral gland, esophagus, gallbladder (mice only), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

## STATISTICAL METHODS

### Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

### Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

## Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are represented as 1-P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

## Analysis of Continuous Variables

Urinary biomarkers were analyzed using Fisher's least significant difference test (Miller, 1960) to make pairwise comparisons. The variance-stabilizing logarithmic transformation was used in the analysis. Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

## Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplastic and nonneoplastic lesions in the rats and mice used in NTP studies. These studies of *p*-nitrotoluene are some of the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions may be affected by the dietary change, use of the existing historical control database (NIH-07 diet) may not be appropriate for all neoplasm types.

Currently, the database includes 11 (10 for male rats) studies by various routes in which the NTP-2000 diet was used. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups regardless of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. For example, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidence of neoplasms are expected. Exceptions exist for some neoplasms/routes, and if comparisons are necessary for these neoplasm types, only studies with similar routes of administration will be used.

## Irradiated Feed

Ionizing energy (irradiation) is known to destroy most, if not all, bacterial and insect contamination without a signficant loss of essential nutrients (Rao and Knapka,

1998). The NTP-2000 diet manufactured and used for the NTP studies was irradiated from May 1996 (fed to rats and mice after June 1996) at the FDA-approved level (25 to 50 kGy) of ionizing radiation. Batches of diets were evaluated for nutrient concentrations before and after irradiation. The concentrations of nutrients and their byproducts of irradiated diets were not substantially different from the same batches before irradiation and nutritionally adequate rodent diets.

## Quality Assurance Methods

The 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

## Genetic Toxicology

The genetic toxicity of *p*-nitrotoluene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and micronucleated erythrocytes in rat and mouse bone marrow. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of *p*-nitrotoluene are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

For mutagenic carcinogens, the combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of DNA and chromosomal effects induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in the acute *in vivo* bone marrow chromosome aberration test or micronucleus test appears to be less than that in the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests are associated with high predictivity for rodent carcinogenicity (Witt *et al*., 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

# RESULTS

## RATS

### *Survival*

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 2). Survival of all exposed groups of rats was as good or better than survival of the control groups.

### *Body Weights, Feed and Compound Consumption, and Clinical Findings*

Mean body weights of 5,000 ppm male and 2,500 female rats were less than those of the controls during most of the study (Tables 7 and 8 and Figure 3); mean body weights of 5,000 ppm females were less than those of the controls throughout the study and were 29% lower than those of controls at the end of the study. Mean body weights of 1,250 ppm females were less during the second year of the study. Feed consumption by 5,000 ppm females was less than that by the control group during the second year of the study (Table H2). Dietary concentrations of 1,250, 2,500, or 5,000 ppm resulted in average daily doses of approximately 55, 110, or 240 mg *p*-nitrotoluene/kg body weight to males and 60, 125, and 265 mg/kg to females. Nasal and eye discharge were observed in exposed male and female rats.

### *Biomarkers of Exposure*

The results of the urinary metabolite determinations in male and female rats are presented in Table F1. The ratios of *p*-acetamidobenzoic acid to creatinine excreted in the urine of male and female rats were generally significantly larger at 2 weeks than at the later time points. The *p*-acetamidobenzoic acid/creatinine ratios were generally linearly related to exposure concentration and were generally larger for females than for males.

The ratios of *p*-nitrobenzoic acid to creatinine were generally significantly larger at 2 weeks than at later time points in males and females. In contrast to the *p*-acetamidobenzoic acid/creatinine ratios, no significant differences were seen between male and female rats. The *p*-nitrobenzoic acid/creatinine ratios were linearly related to exposure concentration.

**TABLE 6**
**Survival of Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 18 | 8 | 10 | 7 |
| Natural deaths | 1 | 4 | 2 | 3 |
| Animals surviving to study termination | 31[a] | 38 | 38 | 40 |
| Percent probability of survival at end of study[b] | 62 | 76 | 76 | 80 |
| Mean survival (days)[c] | 697 | 698 | 714 | 708 |
| Survival analysis[d] | P=0.096N | P=0.269N | P=0.174N | P=0.096N |
| **Female** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 7 | 12 | 10 | 7 |
| Natural deaths | 4 | 1 | 1 | 2 |
| Animals surviving to study termination | 39 | 37 | 39 | 41 |
| Percent probability of survival at end of study | 78 | 74 | 78 | 82 |
| Mean survival (days) | 702 | 706 | 711 | 718 |
| Survival analysis | P=0.507N | P=0.851 | P=1.000N | P=0.725N |

[a] Includes one animal that died during the last week of the study
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

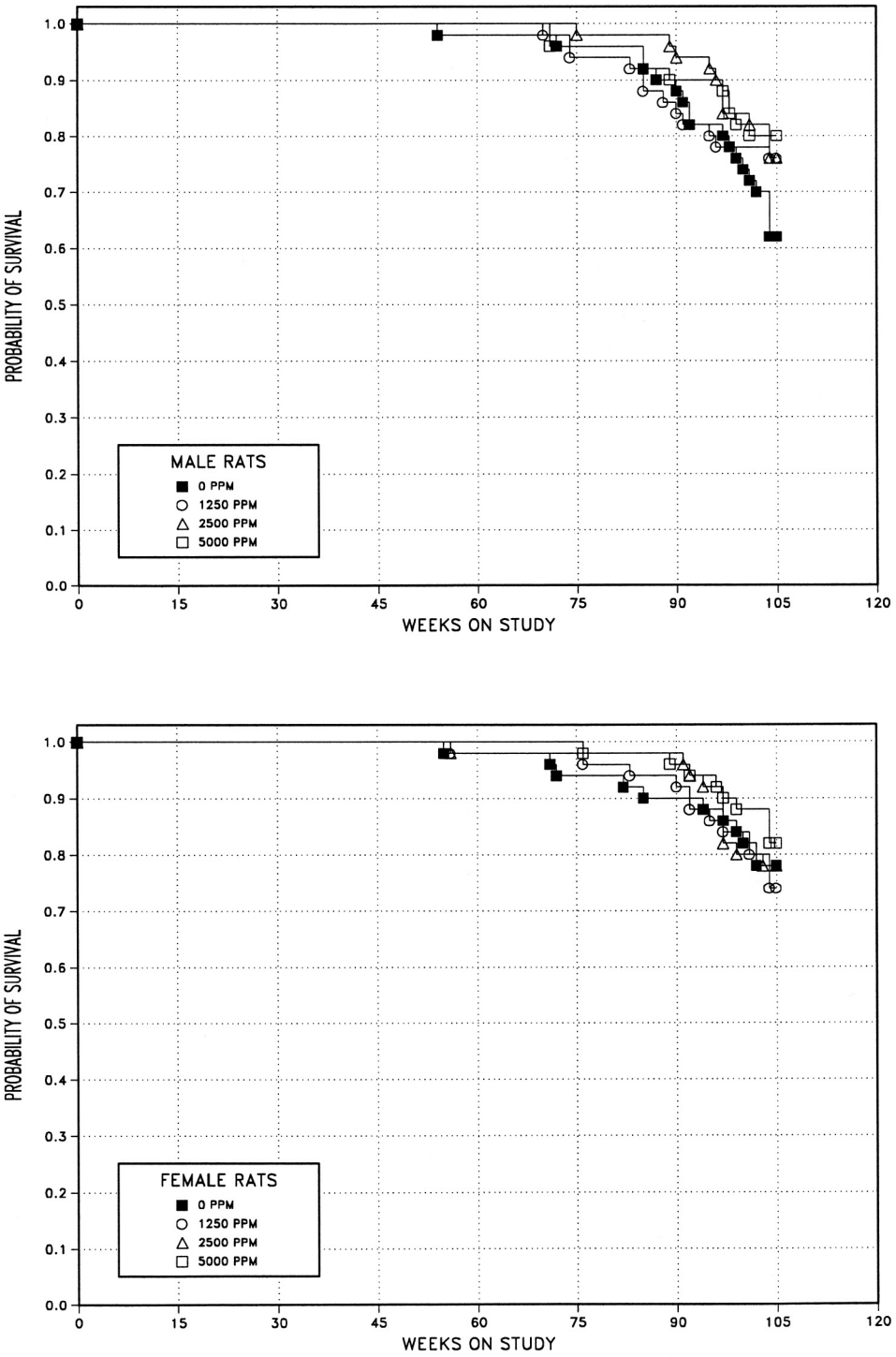



**FIGURE 2**
**Kaplan-Meier Survival Curves for Male and Female Rats Exposed to *p*-Nitrotoluene in Feed for 2 Years**

**TABLE 7**
**Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| Weeks on Study | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 102 | 50 | 102 | 100 | 50 | 103 | 100 | 50 | 101 | 99 | 50 |
| 4 | 206 | 50 | 200 | 97 | 50 | 196 | 95 | 50 | 181 | 88 | 50 |
| 8 | 282 | 50 | 273 | 97 | 50 | 270 | 96 | 50 | 246 | 87 | 50 |
| 12 | 324 | 50 | 319 | 98 | 50 | 310 | 96 | 50 | 283 | 87 | 50 |
| 16 | 352 | 50 | 342 | 97 | 50 | 336 | 96 | 50 | 303 | 86 | 50 |
| 20 | 377 | 50 | 365 | 97 | 50 | 359 | 95 | 50 | 322 | 85 | 50 |
| 24 | 390 | 50 | 381 | 98 | 50 | 368 | 94 | 50 | 335 | 86 | 50 |
| 28 | 405 | 50 | 392 | 97 | 50 | 384 | 95 | 50 | 343 | 85 | 50 |
| 32 | 421 | 50 | 404 | 96 | 50 | 394 | 93 | 50 | 352 | 84 | 50 |
| 36 | 422 | 50 | 410 | 97 | 50 | 403 | 95 | 50 | 362 | 86 | 50 |
| 40 | 426 | 50 | 414 | 97 | 50 | 405 | 95 | 50 | 361 | 85 | 50 |
| 44 | 433 | 50 | 422 | 98 | 50 | 410 | 95 | 50 | 368 | 85 | 50 |
| 48 | 436 | 50 | 426 | 98 | 50 | 418 | 96 | 50 | 370 | 85 | 50 |
| 52 | 438 | 50 | 427 | 97 | 50 | 419 | 96 | 50 | 374 | 85 | 50 |
| 56 | 435 | 49 | 423 | 97 | 50 | 415 | 95 | 50 | 373 | 86 | 50 |
| 60 | 437 | 49 | 430 | 98 | 50 | 419 | 96 | 50 | 378 | 87 | 50 |
| 64 | 440 | 49 | 432 | 98 | 50 | 425 | 97 | 50 | 381 | 87 | 50 |
| 68 | 439 | 49 | 431 | 98 | 50 | 427 | 97 | 50 | 381 | 87 | 50 |
| 72 | 438 | 49 | 428 | 98 | 49 | 425 | 97 | 50 | 385 | 88 | 48 |
| 76 | 440 | 48 | 437 | 99 | 47 | 432 | 98 | 49 | 390 | 89 | 48 |
| 80 | 444 | 48 | 437 | 98 | 47 | 433 | 98 | 49 | 390 | 88 | 48 |
| 84 | 434 | 48 | 434 | 100 | 46 | 430 | 99 | 49 | 387 | 89 | 48 |
| 88 | 432 | 45 | 428 | 99 | 44 | 424 | 98 | 49 | 385 | 89 | 46 |
| 92 | 425 | 43 | 426 | 100 | 41 | 417 | 98 | 47 | 381 | 90 | 45 |
| 96 | 419 | 41 | 420 | 100 | 40 | 412 | 98 | 46 | 380 | 91 | 45 |
| 100 | 410 | 37 | 415 | 101 | 39 | 409 | 100 | 42 | 374 | 91 | 41 |
| 104 | 402 | 33 | 409 | 102 | 39 | 402 | 100 | 41 | 366 | 91 | 40 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 229 | | 224 | 98 | | 220 | 97 | | 203 | 90 | |
| 14-52 | 410 | | 398 | 97 | | 390 | 95 | | 349 | 85 | |
| 53-104 | 430 | | 427 | 99 | | 421 | 98 | | 381 | 89 | |

**TABLE 8**
**Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| Weeks on Study | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 91 | 50 | 90 | 99 | 50 | 91 | 100 | 50 | 92 | 101 | 50 |
| 4 | 144 | 50 | 141 | 98 | 50 | 140 | 98 | 50 | 134 | 94 | 50 |
| 8 | 168 | 50 | 166 | 99 | 50 | 164 | 98 | 50 | 156 | 93 | 50 |
| 12 | 182 | 50 | 179 | 98 | 50 | 176 | 97 | 50 | 167 | 92 | 50 |
| 16 | 192 | 50 | 188 | 98 | 50 | 185 | 96 | 50 | 173 | 90 | 50 |
| 20 | 198 | 50 | 194 | 98 | 50 | 191 | 97 | 50 | 182 | 92 | 50 |
| 24 | 204 | 50 | 200 | 98 | 50 | 196 | 96 | 50 | 185 | 91 | 50 |
| 28 | 211 | 50 | 207 | 98 | 50 | 201 | 96 | 50 | 189 | 90 | 50 |
| 32 | 220 | 50 | 209 | 95 | 50 | 206 | 94 | 50 | 194 | 88 | 50 |
| 36 | 223 | 50 | 216 | 97 | 50 | 212 | 95 | 50 | 198 | 89 | 50 |
| 40 | 224 | 50 | 216 | 96 | 50 | 213 | 95 | 50 | 196 | 87 | 50 |
| 44 | 232 | 50 | 222 | 96 | 50 | 216 | 93 | 50 | 198 | 86 | 50 |
| 48 | 234 | 50 | 224 | 96 | 50 | 218 | 93 | 50 | 198 | 85 | 50 |
| 52 | 236 | 50 | 227 | 96 | 50 | 220 | 93 | 50 | 201 | 85 | 50 |
| 56 | 243 | 49 | 231 | 95 | 49 | 225 | 92 | 49 | 201 | 83 | 50 |
| 60 | 250 | 49 | 236 | 94 | 49 | 226 | 91 | 49 | 202 | 81 | 50 |
| 64 | 258 | 49 | 239 | 93 | 49 | 232 | 90 | 49 | 203 | 79 | 50 |
| 68 | 263 | 49 | 249 | 95 | 49 | 238 | 90 | 49 | 206 | 78 | 50 |
| 72 | 270 | 48 | 253 | 94 | 49 | 241 | 89 | 49 | 207 | 77 | 50 |
| 76 | 277 | 47 | 260 | 94 | 48 | 249 | 90 | 49 | 208 | 75 | 50 |
| 80 | 285 | 47 | 267 | 94 | 48 | 257 | 90 | 49 | 213 | 75 | 49 |
| 84 | 288 | 46 | 268 | 93 | 47 | 261 | 91 | 49 | 212 | 73 | 49 |
| 88 | 293 | 45 | 269 | 92 | 47 | 262 | 89 | 49 | 210 | 72 | 49 |
| 92 | 295 | 45 | 272 | 92 | 44 | 262 | 89 | 47 | 212 | 72 | 47 |
| 96 | 293 | 44 | 269 | 92 | 43 | 262 | 89 | 46 | 211 | 72 | 47 |
| 100 | 293 | 41 | 272 | 93 | 42 | 266 | 91 | 40 | 212 | 72 | 44 |
| 104 | 294 | 39 | 272 | 92 | 38 | 267 | 91 | 39 | 210 | 71 | 42 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 146 | | 144 | 99 | | 143 | 98 | | 137 | 95 | |
| 14-52 | 217 | | 210 | 97 | | 206 | 95 | | 191 | 88 | |
| 53-104 | 277 | | 258 | 93 | | 250 | 90 | | 208 | 75 | |

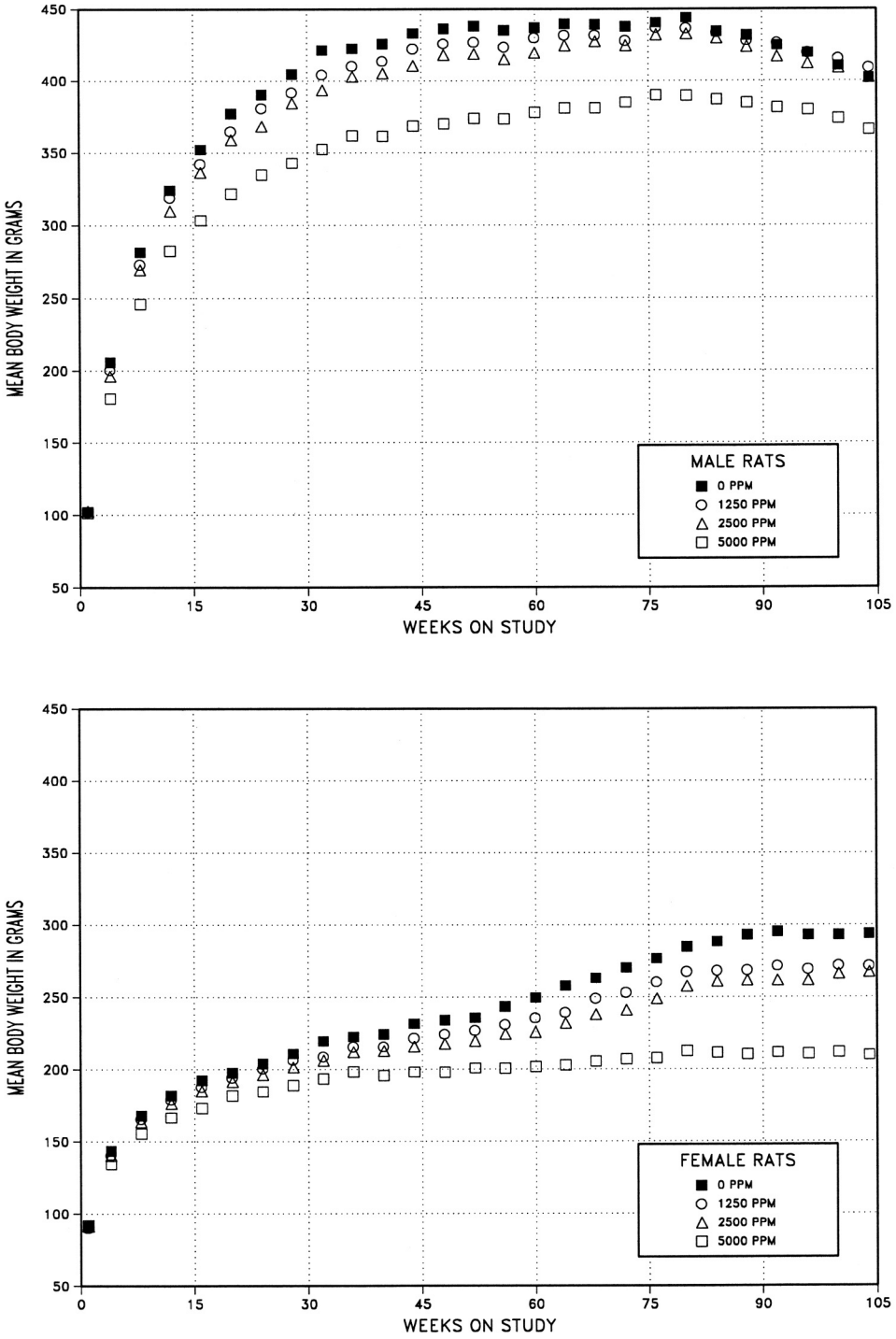



**FIGURE 3**
**Growth Curves for Male and Female Rats Exposed to *p*-Nitrotoluene in Feed for 2 Years**

## *Pathology and Statistical Analyses*

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms and/or nonneoplastic lesions of the clitoral gland, skin, kidney, spleen, liver, testis, uterus, mammary gland, pancreatic islets, and thyroid gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

*Clitoral Gland:* The incidence of adenoma or carcinoma (combined) in 2,500 ppm females was significantly greater than that in the controls, and the incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) generally exceeded the historical ranges in controls (all routes) given NTP-2000 diet and, except for carcinoma, in untreated controls given NIH-07 diet for 2 years (Tables 9, B3, and B4a). Proliferative lesions of the clitoral gland (hyperplasia, adenoma, and carcinoma) constitute a morphologic and biologic continuum. Compression and distortion of the acinar architecture generally distinguish neoplasms from hyperplasia, with carcinomas being larger and having more irregular borders than adenomas. In the current study, the increased

**TABLE 9**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral Gland in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| Number Examined Microscopically | 50 | 50 | 50 | 49 |
| Hyperplasia[a] | 3 (4.0)[b] | 5 (2.8) | 4 (3.3) | 6 (3.0) |
| Adenoma (includes multiple)[c] | 7 | 8 | 15 | 6 |
| Carcinoma (includes multiple)[d] | 2 | 4 | 6 | 2 |
| Adenoma or Carcinoma[e] | | | | |
| Overall rate[f] | 8/50 (16%) | 12/50 (24%) | 20/50 (40%) | 8/49 (16%) |
| Adjusted rate[g] | 17.4% | 25.9% | 41.5% | 16.9% |
| Terminal rate[h] | 8/39 (21%) | 11/37 (30%) | 18/39 (46%) | 8/41 (20%) |
| First incidence (days) | 729 (T) | 701 | 387 | 729 (T) |
| Poly-3 test[i] | P=0.487N | P=0.232 | P=0.008 | P=0.580N |

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 74/636 (11.1% ± 5.9%), range 2%-20%; with controls given NIH-07 diet: 89/968 (9.2% ± 6.0%), range 0%-22%
[d] Historical incidence for NTP-2000 diet: 11/636 (1.9% ± 2.2%), range 0%-6%; for NIH-07 diet: 30/968 (3.1% ± 3.2%), range 0%-12%
[e] Historical incidence for NTP-2000 diet: 84/636 (12.8% ± 7.4%), range 2%-24%; for NIH-07 diet: 118/968 (12.2% ± 7.7%), range 2%-35%
[f] Number of animals with neoplasm per number of animals with clitoral gland examined microscopically
[g] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[h] Observed incidence at terminal kill
[i] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

incidence of carcinoma in 2,500 ppm females was not accompanied by corresponding significant increases in the incidences of hyperplasia or adenoma.

*Skin:* The incidences of subcutaneous fibroma and of subcutaneous fibroma or fibrosarcoma (combined) in 2,500 ppm males were significantly greater than those in controls and exceeded the historical ranges in untreated control male rats given NTP-2000 diet or NIH-07 diet for 2 years (Tables 10, A3, and A4a). Fibromas were identified grossly at necropsy as large masses in the subcutis that microscopically were composed of scattered spindle cells separated by abundant collagenous matrix.

**TABLE 10**
**Incidences of Neoplasms of the Skin (Subcutaneous) in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| Fibroma[a] | | | | |
| Overall rate[b] | 1/50 (2%) | 2/50 (4%) | 7/50 (14%) | 1/50 (2%) |
| Adjusted rate[c] | 2.2% | 4.4% | 14.7% | 2.1% |
| Terminal rate[d] | 0/31 (0%) | 2/38 (5%) | 5/38 (13%) | 0/40 (0%) |
| First incidence (days) | 695 | 729 (T) | 676 | 591 |
| Poly-3 test[e] | P=0.561 | P=0.500 | P=0.037 | P=0.751N |
| Fibroma or Fibrosarcoma[f] | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 9/50 (18%) | 1/50 (2%) |
| Adjusted rate | 2.2% | 4.5% | 18.8% | 2.1% |
| Terminal rate | 0/31 (0%) | 2/38 (5%) | 5/38 (13%) | 0/40 (0%) |
| First incidence (days) | 695 | 729 (T) | 676 | 591 |
| Poly-3 test | P=0.525 | P=0.500 | P=0.011 | P=0.751N |

(T)Terminal sacrifice
[a] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 33/609 (5.1% ± 4.0%), range 0%-12%; with controls given NIH-07 diet: 56/1,004 (5.6% ± 3.2%), range 0%-10%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[f] Historical incidence for NTP-2000 diet: 41/609 (6.3% ± 4.2%), range 2%-14%; for NIH-07 diet: 65/1,004 (6.5% ± 3.1%), range 2%-10%

*Kidney:* Renal changes associated with *p*-nitrotoluene exposure consisted of increased incidences of renal tubule hyaline droplet accumulation and pigmentation in all exposed groups of males and females (Tables 11, A5, and B5). The hyaline droplets consisted of variably sized, spherical eosinophilic to rust-colored globules within the cytoplasm of cortical tubule epithelial cells. The incidences of hyaline droplets were higher in females than in males, but there was no clear exposure concentration-related response in either gender. Histochemically, the globules in both control and exposed rats tended to be positive for protein by the Mallory-Heidenhain stain and variably positive with periodic acid-Schiff and acid-fast staining. Pigmentation was generally seen in cortical tubule cells but was distinguished from hyaline droplets as coarser, granular brown-staining cytoplasmic inclusions. The incidence and severity of pigmentation generally increased with increasing exposure concentration. With special stains, the pigment was acid-fast positive but negative for bile (Hall's stain) and iron (Prussian blue reaction) and therefore interpreted to be predominantly lipofuscin pigment. Additional findings in the kidney were considered related to exposure. The incidence and severity of renal mineralization increased with increasing exposure concentration in females. Mineralization is common, particularly in females, and appears as basophilic concretions in the distal tubules. The incidence of chronic nephropathy in 5,000 ppm males was decreased. Nephropathy is a common lesion in aging rats and encompasses a spectrum of changes including interstitial inflammation, tubule degeneration and regeneration, and glomerular thickening. The incidence of renal tubule oncocytic hyperplasia in 5,000 ppm females was increased. Oncocytic hyperplasia was characterized by individual tubules that were slightly enlarged and filled by large polygonal epithelial cells containing abundant eosinophilic granular cytoplasm and centrally located nuclei (oncocytes). Oncocytic proliferation is thought to arise from the distal renal tubule and is not a part of the spectrum of lesions in the development of proximal tubule neoplasms. No oncocytic neoplasms were observed in the current study.

**TABLE 11**
**Incidences of Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | | 1,250 ppm | | 2,500 ppm | | 5,000 ppm | |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| Number Examined Microscopically | 50 | | 50 | | 50 | | 50 | |
| Renal Tubule, Hyaline Droplet[a] | 2 | (2.0)[b] | 23** | (1.9) | 27** | (2.0) | 18** | (2.5) |
| Renal Tubule, Pigmentation | 10 | (2.3) | 28** | (1.5) | 47** | (1.8) | 46** | (2.4) |
| Renal Tubule, Hyperplasia, Oncocytic | 0 | | 0 | | 0 | | 3 | (3.7) |
| Nephropathy | 33 | (1.1) | 37 | (1.1) | 31 | (1.0) | 18* | (1.0) |
| **Female** | | | | | | | | |
| Number Examined Microscopically | 50 | | 50 | | 50 | | 50 | |
| Renal Tubule, Hyaline Droplet | 8 | (1.8) | 41** | (2.1) | 49** | (2.2) | 46** | (2.4) |
| Renal Tubule, Pigmentation | 9 | (1.7) | 43** | (1.5) | 49** | (1.9) | 50** | (2.6) |
| Mineralization | 15 | (1.1) | 21 | (1.1) | 32** | (1.3) | 40** | (1.8) |
| Renal Tubule, Hyperplasia, Oncocytic | 0 | | 2 | (1.0) | 4 | (1.3) | 6* | (1.2) |

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

*Spleen:* The incidences of hematopoietic cell proliferation and pigmentation in the spleen increased with exposure concentration in males; incidences of these lesions in females were increased relative to controls in the 2,500 and 5,000 ppm groups (Tables 12, A5, and B5). The pigment was iron-positive by the Prussian blue method and therefore considered to be hemosiderin. Hematopoiesis and hemosiderin pigment are normal findings in the spleen of rats; their incidences may increase with aging or enhanced erythrocyte destruction. These treatment-related splenic changes at 2 years were the same as those seen in the 13-week study of *p*-nitrotoluene and were attributed to hemotoxicity.

*Liver:* Significantly increased incidences of various types of altered cell foci in the liver of males and females were associated with exposure (Tables 13, A5, and B5). Incidences of basophilic and clear cell foci were increased in the 2,500 and 5,000 ppm males, and incidences of eosinophilic foci were increased in 5,000 ppm males and 2,500 and 5,000 ppm females. Liver foci are common spontaneous changes in aging rats and may be further induced by chemical exposure. However, the increased occurrence of foci in the current study may have been related to the decreased incidences of mononuclear cell leukemia. Leukemic infiltration of the liver often obscures the altered liver cell foci, and consequently the decreased incidences of leukemia may have led to greater detection of foci (Maronpot *et al*., 1989).

*Mononuclear Cell Leukemia:* The incidences of mononuclear cell leukemia in all groups of exposed males and in 2,500 and 5,000 ppm females were significantly less than those in the controls (Tables 14, A3, and B3). The decreased incidences were particularly evident in the liver and spleen, which are the organs most commonly affected by mononuclear cell leukemia, and the incidences were less than the historical ranges for this neoplasm in controls given NTP-2000 diet and in untreated controls given NIH-07 diet for 2 years (Tables 14, A4b, and B4b).

**TABLE 12**
**Incidences of Nonneoplastic Lesions of the Spleen in Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | | 1,250 ppm | | 2,500 ppm | | 5,000 ppm | |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| Number Examined Microscopically | 50 | | 50 | | 50 | | 50 | |
| Hematopoietic Cell Proliferation[a] | 9 | (2.0)[b] | 13 | (1.9) | 19* | (1.4) | 25** | (1.5) |
| Pigmentation | 10 | (2.1) | 12 | (2.4) | 24** | (2.5) | 38** | (2.6) |
| **Female** | | | | | | | | |
| Number Examined Microscopically | 50 | | 50 | | 50 | | 50 | |
| Hematopoietic Cell Proliferation | 26 | (1.8) | 26 | (1.8) | 45** | (1.9) | 43** | (1.9) |
| Pigmentation | 24 | (2.3) | 32 | (2.6) | 45** | (2.8) | 48** | (2.9) |

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

**TABLE 13**
**Incidences of Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Basophilic Focus[a] | 31 | 39 | 42* | 45** |
| Clear Cell Focus | 20 | 27 | 30* | 32* |
| Eosinophilic Focus | 5 | 5 | 5 | 19** |
| **Female** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Eosinophilic Focus | 1 | 2 | 7* | 9* |

* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion

**TABLE 14**
**Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| Mononuclear Cell Leukemia[a] | | | | |
| Overall rate[b] | 24/50 (48%) | 12/50 (24%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted rate[c] | 51.6% | 25.7% | 10.5% | 8.6% |
| Terminal rate[d] | 13/31 (42%) | 7/38 (18%) | 3/38 (8%) | 2/40 (5%) |
| First incidence (days) | 592 | 581 | 668 | 685 |
| Poly-3 test[e] | P<0.001N | P=0.007N | P<0.001N | P<0.001N |
| **Female** | | | | |
| Mononuclear Cell Leukemia[f] | | | | |
| Overall rate | 13/50 (26%) | 12/50 (24%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 27.7% | 24.5% | 6.3% | 2.1% |
| Terminal rate | 10/39 (26%) | 5/37 (14%) | 1/39 (3%) | 1/41 (2%) |
| First incidence (days) | 380 | 387 | 676 | 729 (T) |
| Poly-3 test | P<0.001N | P=0.450N | P=0.005N | P<0.001N |

(T)Terminal sacrifice
[a] Historical incidence for 2-year studies with control groups given NTP-2000 diet (mean ± standard deviation): 300/609 (47.3% ± 10.5%), range 32%-68%; with controls given NIH-07 diet: 547/1,004 (54.5% ± 10.7%), range 32%-74%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group in indicated by **N**.
[f] Historical incidence for NTP-2000 diet: 185/659 (29.1% ± 8.4%), range 16%-42%; for NIH-07 diet: 293/1,001 (29.3% ± 7.6%), range 16%-47%

*Testis:* In 5,000 ppm males, the incidence of interstitial cell adenoma was significantly decreased and was less than the historical range in untreated controls given NTP-2000 diet or NIH-07 diet for 2 years (Tables 15, A3, and A4c). Interstitial cell hyperplasia and adenoma are common lesions in F344/N rats and are found, usually bilaterally, in most control animals in 2-year studies. In the current study, the decreased incidence of adenoma in 5,000 ppm males was associated with a decrease in the proportion of animals with bilateral neoplasms, as well as with an increased incidence of interstitial cell hyperplasia. Because hyperplasia, unilateral adenoma, and bilateral adenoma of this cell type represent a morphologic and biologic continuum, these data indicate a delayed progression of proliferative interstitial cell lesions associated with chemical exposure.

The incidence of atrophy of the germinal epithelium was significantly increased in 5,000 ppm males (Tables 15 and A5). This change was moderate to marked in severity and was characterized by partial to complete loss of spermatogenic cells lining the seminiferous tubules. The increased incidence of atrophy may have been partly attributable to the decreased neoplasm incidences described above because atrophic change may be more apparent in the absence of neoplasms. However, the severity and bilateral nature of the atrophic change in exposed rats suggest a direct chemical effect.

*Uterus:* The incidences of endometrial cystic hyperplasia in 2,500 and 5,000 ppm females were significantly greater than that in the controls (5/50, 10/50, 13/50, 19/50; Table B5). This change encompassed a spectrum of lesions, ranging from slight increases in size and number of endometrial glands to more severe cystic change with dilatation of the uterine lumen (hydrometra). Endometrial hyperplasia is not considered a preneoplastic change in F344/N rats, and in the current study it was not associated with any uterine neoplastic effects.

**TABLE 15**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Interstitial Cell Hyperplasia[a] | 7 (1.9)[b] | 15* (1.7) | 7 (1.9) | 23** (2.3) |
| Germinal Epithelial Atrophy | 7 (2.1) | 11 (2.7) | 8 (3.1) | 30** (3.5) |
| Interstitial Cell Adenoma, Bilateral | 40 | 32 | 39 | 17 |
| Interstitial Cell Adenoma, Unilateral | 9 | 14 | 6 | 17 |
| Interstitial Cell Adenoma (bilateral or unilateral)[c] | | | | |
| Overall rate[d] | 49/50 (98%) | 46/50 (92%) | 45/50 (90%) | 34/50 (68%) |
| Adjusted rate[e] | 99.7% | 93.6% | 92.7% | 72.5% |
| Terminal rate[f] | 31/31 (100%) | 36/38 (95%) | 37/38 (97%) | 31/40 (78%) |
| First incidence (days) | 504 | 490 | 621 | 685 |
| Poly-3 test[g] | P<0.001N | P=0.110N | P=0.066N | P<0.001N |

* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 535/609 (86.4% ± 9.1%), range 72%-98%; with controls given NIH-07 diet: 889/1,003 (88.6% ± 6.0%), range 74%-96%
[d] Number of animals with neoplasm per number of animals examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

*Mammary Gland:* The incidence of mammary gland fibroadenoma was significantly decreased in 5,000 ppm female rats and was less than the historical ranges in untreated controls given NTP-2000 diet or NIH-07 diet for 2 years (Tables 16, B3, and B4c). The lower incidence may have been related to the lower body weights in this group. The incidence of mammary gland hyperplasia, a possible precursor to fibroadenoma, was also significantly decreased in 5,000 ppm females.

*Decreased Neoplasm Incidences:* The incidence of pancreatic islet adenoma or carcinoma (combined) occurred with a negative trend in males, and the incidences in the 1,250 and 5,000 ppm groups were significantly decreased (5/50, 0/50, 1/49, 0/50; Table A3). The incidence of thyroid gland C-cell adenoma occurred with a negative trend in males, and the incidence in the 5,000 ppm group was significantly decreased (11/50, 7/50, 5/50, 4/50; Table A3). However, the decreased incidences were within historical control ranges for both neoplasms in controls given NTP-2000 diet [pancreatic islet adenoma or carcinoma (combined): 31/607 (5.5% ± 4.0%), range 0%-12%; thyroid gland C-cell adenoma: 92/603 (15.6% ± 6.3%), range 2%-24%] and untreated controls given NIH-07 diet [pancreatic islet adenoma or carcinoma (combined): 46/997 (4.6% ± 3.3%), range 0%-10%; thyroid gland C-cell adenoma: 116/1,002 (11.6% ± 5.9%), range 2%-24%], and therefore the relationship of these findings to *p*-nitrotoluene exposure was uncertain.

**TABLE 16**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| Number Necropsied | 50 | 50 | 50 | 50 |
| Hyperplasia[a] | 42 (2.4)[b] | 42 (2.5) | 45 (2.4) | 29** (1.9) |
| Fibroadenoma[c] | | | | |
| Overall rate[d] | 14/50 (28%) | 17/50 (34%) | 20/50 (40%) | 5/50 (10%) |
| Adjusted rate[e] | 30.2% | 36.6% | 41.5% | 10.4% |
| Terminal rate[f] | 11/39 (28%) | 14/37 (38%) | 15/39 (39%) | 4/41 (10%) |
| First incidence (days) | 655 | 701 | 633 | 676 |
| Poly-3 test[g] | P=0.008N | P=0.331 | P=0.176 | P=0.014N |

** Significantly different (P≤0.01) from the control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 284/659 (41.1% ± 10.1%), range 28%-56%; with controls given NIH-07 diet: 431/1,001 (43.1% ± 10.7%), range 24%-60%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

# MICE

## *Survival*

Estimates of 2-year survival probabilities for male and female mice are shown in Table 17 and in the Kaplan-Meier survival curves (Figure 4). Survival of all exposed groups of mice was similar to that of the control groups.

## *Body Weights, Feed and Compound Consumption, and Clinical Findings*

Mean body weights of 5,000 ppm males and females were less than those of the control groups during most of the study (Tables 18 and 19 and Figure 5). Mean body weights of 2,500 ppm males were less than those of the controls after week 92. Feed consumption by all exposed groups of mice was similar to that by the control groups (Tables H3 and H4). Dietary concentrations of 1,250, 2,500, or 5,000 ppm resulted in average daily doses of approximately 170, 345, or 690 mg *p*-nitrotoluene/kg body weight to males and 155, 315, or 660 mg/kg to females. No clinical findings were attributed to *p*-nitrotoluene exposure.

## *Biomarkers of Exposure*

The results of metabolite determinations in male and female mice are presented in Table F2. At time points with sufficient data to make determinations, the ratios of metabolite to creatinine appear to be linearly related to exposure concentration. In some cases, there was insufficient urine for analysis, or the metabolite concentration was below the limit of quantitation.

**TABLE 17**
**Survival of Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 2 | 2 | 3 | 6 |
| Natural deaths | 2 | 2 | 2 | 2 |
| Animals surviving to study termination | 46 | 46 | 45 | 42 |
| Percent probability of survival at end of study[a] | 92 | 92 | 90 | 84 |
| Mean survival (days)[b] | 722 | 719 | 720 | 715 |
| Survival analysis[c] | P=0.187 | P=1.000 | P=0.974 | P=0.341 |
| **Female** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 2 | 1 | 5 | 1 |
| Natural deaths | 2 | 2 | 2 | 0 |
| Animals surviving to study termination | 46 | 47 | 43[d] | 49 |
| Percent probability of survival at end of study | 92 | 94 | 86 | 98 |
| Mean survival (days) | 724 | 722 | 715 | 720 |
| Survival analysis | P=0.452N | P=1.000N | P=0.509 | P=0.366N |

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[d] Includes two animals that died during the last week of study

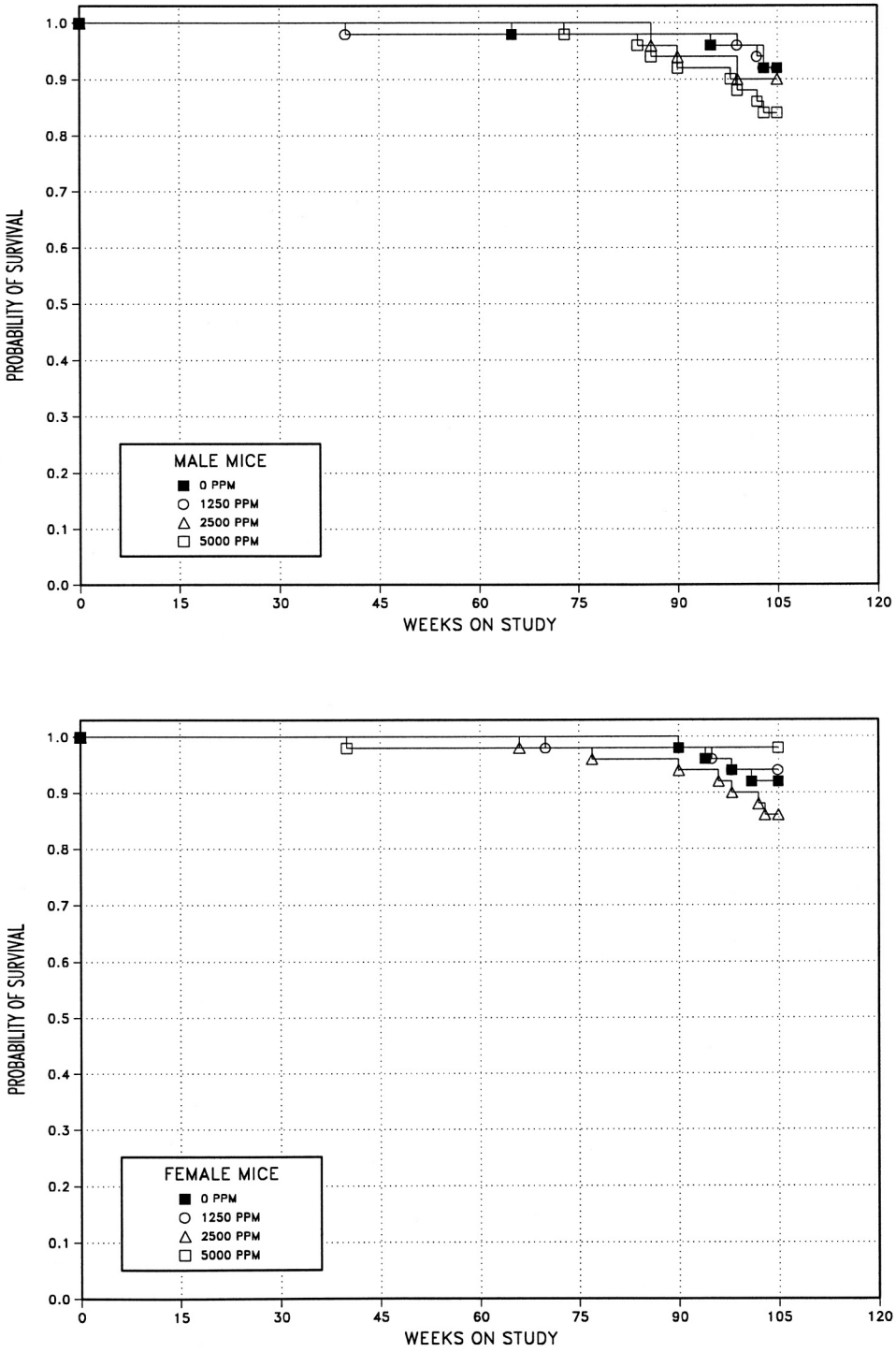



**FIGURE 4**
**Kaplan-Meier Survival Curves for Male and Female Mice Exposed to *p*-Nitrotoluene in Feed for 2 Years**

**TABLE 18**
**Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| Weeks on Study | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 20.3 | 50 | 20.2 | 100 | 50 | 20.4 | 101 | 50 | 20.3 | 100 | 50 |
| 4 | 24.4 | 50 | 24.3 | 100 | 50 | 24.4 | 100 | 50 | 23.8 | 98 | 50 |
| 8 | 27.9 | 50 | 27.5 | 99 | 50 | 27.7 | 99 | 50 | 26.9 | 96 | 50 |
| 12 | 31.6 | 50 | 31.3 | 99 | 50 | 31.5 | 100 | 50 | 30.3 | 96 | 50 |
| 16 | 34.8 | 50 | 34.5 | 99 | 50 | 34.4 | 99 | 50 | 33.1 | 95 | 50 |
| 20 | 37.7 | 50 | 37.5 | 100 | 50 | 37.3 | 99 | 50 | 35.8 | 95 | 50 |
| 24 | 39.4 | 50 | 39.0 | 99 | 50 | 38.7 | 98 | 50 | 36.9 | 94 | 50 |
| 28 | 40.8 | 50 | 40.7 | 100 | 50 | 40.1 | 98 | 50 | 39.0 | 96 | 50 |
| 32 | 42.4 | 50 | 42.2 | 100 | 50 | 41.7 | 98 | 50 | 40.7 | 96 | 50 |
| 36 | 43.0 | 50 | 43.1 | 100 | 50 | 42.1 | 98 | 50 | 41.3 | 96 | 50 |
| 40 | 43.8 | 50 | 43.7 | 100 | 50 | 43.1 | 98 | 50 | 41.3 | 94 | 50 |
| 44 | 44.7 | 50 | 44.9 | 100 | 49 | 44.0 | 98 | 50 | 41.9 | 94 | 50 |
| 48 | 45.4 | 50 | 44.8 | 99 | 49 | 43.9 | 97 | 50 | 42.3 | 93 | 50 |
| 52 | 45.2 | 50 | 44.7 | 99 | 49 | 43.4 | 96 | 50 | 42.1 | 93 | 50 |
| 56 | 45.8 | 50 | 45.5 | 99 | 49 | 44.4 | 97 | 50 | 42.5 | 93 | 50 |
| 60 | 45.8 | 50 | 45.9 | 100 | 49 | 44.0 | 96 | 50 | 42.1 | 92 | 50 |
| 64 | 47.1 | 50 | 47.3 | 100 | 49 | 45.1 | 96 | 50 | 43.1 | 92 | 50 |
| 68 | 47.4 | 49 | 47.7 | 101 | 49 | 45.6 | 96 | 50 | 43.1 | 91 | 50 |
| 72 | 46.8 | 49 | 47.1 | 101 | 49 | 45.4 | 97 | 50 | 42.4 | 91 | 50 |
| 76 | 45.5 | 49 | 46.6 | 102 | 49 | 44.5 | 98 | 50 | 42.5 | 93 | 49 |
| 80 | 46.3 | 49 | 47.2 | 102 | 49 | 45.2 | 98 | 50 | 42.8 | 92 | 49 |
| 84 | 46.7 | 49 | 47.5 | 102 | 49 | 45.4 | 97 | 50 | 42.4 | 91 | 49 |
| 88 | 45.5 | 49 | 46.0 | 101 | 49 | 44.4 | 98 | 48 | 42.1 | 93 | 47 |
| 92 | 45.1 | 49 | 45.4 | 101 | 49 | 43.9 | 97 | 47 | 42.0 | 93 | 46 |
| 96 | 43.0 | 48 | 42.3 | 98 | 49 | 40.5 | 94 | 47 | 39.0 | 91 | 46 |
| 100 | 41.7 | 48 | 40.3 | 97 | 48 | 38.8 | 93 | 45 | 37.5 | 90 | 44 |
| 104 | 41.3 | 46 | 39.7 | 96 | 46 | 37.3 | 90 | 45 | 36.2 | 88 | 42 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 26.1 | | 25.8 | 99 | | 26.0 | 100 | | 25.3 | 98 | |
| 14-52 | 41.7 | | 41.5 | 100 | | 40.9 | 98 | | 39.4 | 95 | |
| 53-104 | 45.2 | | 45.3 | 100 | | 43.4 | 96 | | 41.4 | 92 | |

**TABLE 19**
**Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| Weeks on Study | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | 15.5 | 50 | 15.5 | 100 | 50 | 16.6 | 107 | 50 | 16.4 | 106 | 50 |
| 4 | 18.1 | 50 | 19.2 | 106 | 50 | 19.3 | 107 | 50 | 18.4 | 102 | 50 |
| 8 | 21.7 | 50 | 22.4 | 103 | 50 | 22.2 | 102 | 50 | 20.9 | 96 | 50 |
| 12 | 25.1 | 50 | 26.5 | 106 | 50 | 25.9 | 103 | 50 | 23.3 | 93 | 50 |
| 16 | 28.2 | 50 | 28.2 | 100 | 50 | 27.9 | 99 | 50 | 24.7 | 88 | 50 |
| 20 | 30.8 | 50 | 29.9 | 97 | 50 | 30.1 | 98 | 50 | 26.4 | 86 | 50 |
| 24 | 32.2 | 50 | 32.8 | 102 | 50 | 33.0 | 103 | 50 | 28.2 | 88 | 50 |
| 28 | 34.2 | 50 | 34.6 | 101 | 50 | 33.8 | 99 | 50 | 28.7 | 84 | 50 |
| 32 | 34.7 | 50 | 36.4 | 105 | 50 | 34.8 | 100 | 50 | 29.7 | 86 | 50 |
| 36 | 36.3 | 50 | 37.4 | 103 | 50 | 36.5 | 101 | 50 | 31.1 | 86 | 50 |
| 40 | 36.2 | 50 | 38.0 | 105 | 50 | 37.2 | 103 | 50 | 31.6 | 87 | 50 |
| 44 | 36.2 | 50 | 38.5 | 106 | 50 | 36.9 | 102 | 50 | 32.2 | 89 | 49 |
| 48 | 38.9 | 50 | 40.8 | 105 | 50 | 39.7 | 102 | 50 | 33.6 | 86 | 49 |
| 52 | 38.5 | 50 | 39.2 | 102 | 50 | 39.4 | 102 | 50 | 33.2 | 86 | 49 |
| 56 | 38.4 | 50 | 39.7 | 103 | 50 | 39.5 | 103 | 50 | 33.5 | 87 | 49 |
| 60 | 37.9 | 50 | 39.0 | 103 | 50 | 38.5 | 102 | 50 | 33.6 | 89 | 49 |
| 64 | 39.0 | 50 | 41.2 | 106 | 50 | 40.0 | 103 | 50 | 34.9 | 90 | 49 |
| 68 | 39.1 | 50 | 41.6 | 106 | 50 | 40.8 | 104 | 49 | 34.6 | 89 | 49 |
| 72 | 38.9 | 50 | 40.7 | 105 | 49 | 40.2 | 103 | 49 | 33.8 | 87 | 49 |
| 76 | 38.0 | 50 | 41.0 | 108 | 49 | 39.6 | 104 | 49 | 34.4 | 91 | 49 |
| 80 | 39.2 | 50 | 42.0 | 107 | 49 | 41.3 | 105 | 48 | 35.1 | 90 | 49 |
| 84 | 41.4 | 50 | 44.1 | 107 | 49 | 42.4 | 102 | 48 | 34.9 | 84 | 49 |
| 88 | 39.3 | 50 | 41.5 | 106 | 49 | 40.0 | 102 | 48 | 34.6 | 88 | 49 |
| 92 | 39.3 | 49 | 40.7 | 104 | 49 | 41.5 | 106 | 47 | 34.7 | 88 | 49 |
| 96 | 39.2 | 48 | 40.4 | 103 | 48 | 39.1 | 100 | 47 | 33.7 | 86 | 49 |
| 100 | 38.9 | 47 | 39.3 | 101 | 47 | 40.2 | 103 | 45 | 34.7 | 89 | 49 |
| 104 | 38.5 | 46 | 39.1 | 102 | 47 | 38.9 | 101 | 43 | 32.9 | 86 | 49 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 20.1 | | 20.9 | 104 | | 21.0 | 105 | | 19.8 | 99 | |
| 14-52 | 34.6 | | 35.6 | 103 | | 34.9 | 101 | | 29.9 | 87 | |
| 53-104 | 39.0 | | 40.8 | 105 | | 40.2 | 103 | | 34.3 | 88 | |

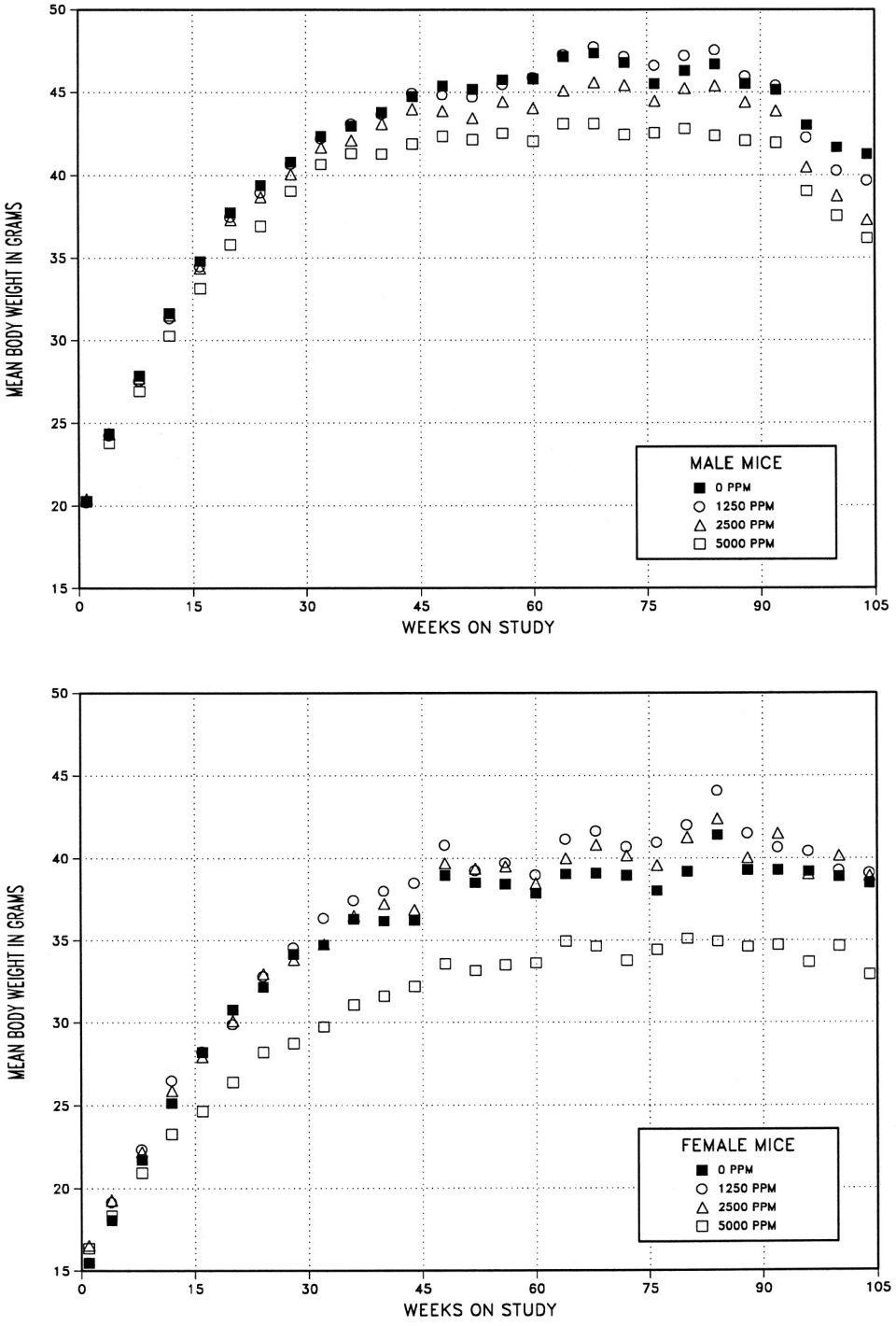



**FIGURE 5**
**Growth Curves for Male and Female Mice Exposed to *p*-Nitrotoluene for 2 Years**

## *Pathology and Statistical Analyses*

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

*Lung:* The combined incidence of alveolar/bronchiolar adenoma or carcinoma was significantly increased in 5,000 ppm males and exceeded the historical control range from feed studies using the NIH-07 diet (Tables 20, C3, and C4). The highest incidence seen in male controls (all routes) from studies using the NTP-2000 diet is 22/50 (44%) and the average incidence in NTP-2000 diet studies was 27% (Table C4). The incidence of alveolar epithelial hyperplasia, which is considered a precursor lesion to alveolar/bronchiolar adenoma and carcinoma was increased in 5,000 ppm males, although the increase was not statistically

**TABLE 20**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Alveolar Epithelium, Bronchiolization[a] | 0 | 20** (1.1)[b] | 30** (1.2) | 48** (1.4) |
| Alveolar Epithelium, Hyperplasia | 1 (2.0) | 1 (2.0) | 4 (1.5) | 6 (2.7) |
| Alveolar/bronchiolar Adenoma (includes multiple) | 6 | 9 | 8 | 13 |
| Alveolar/bronchiolar Carcinoma (includes multiple) | 2 | 6 | 4 | 6 |
| Alveolar/bronchiolar Adenoma or Carcinoma[c] | | | | |
| Overall rate[d] | 8/50 (16%) | 14/50 (28%) | 12/50 (24%) | 19/50 (38%) |
| Adjusted rate[e] | 16.3% | 28.6% | 24.7% | 38.4% |
| Terminal rate[f] | 6/46 (13%) | 12/46 (26%) | 11/45 (24%) | 14/42 (33%) |
| First incidence (days) | 665 | 689 | 693 | 505 |
| Poly-3 test[g] | P=0.014 | P=0.111 | P=0.217 | P=0.011 |
| **Female** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Alveolar Epithelium, Bronchiolization | 0 | 33** (1.0) | 41** (1.3) | 49** (1.5) |
| Alveolar Epithelium, Hyperplasia | 2 (2.0) | 1 (2.0) | 2 (1.0) | 1 (1.0) |
| Alveolar/bronchiolar Adenoma | 5 | 2 | 2 | 5 |
| Alveolar/bronchiolar Carcinoma | 1 | 0 | 2 | 3 |
| Alveolar/bronchiolar Adenoma or Carcinoma | 6 | 2 | 4 | 8 |

** Significantly different ($P \leq 0.01$) from the control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 176/659 (27.1% ± 9.3%), range 12%-44%; with controls given NIH-07 diet: 236/952 (24.8% ± 7.0%), range 12%-36%
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

significant (Tables 20 and C5). Morphologically, the lesions in this biologic continuum progress from focal proliferations of cuboidal cells lining alveoli (hyperplasia) to solid nodules composed of monomorphic (adenoma) to pleomorphic (carcinoma) cells. There were no significant increases in the incidences of alveolar/bronchiolar neoplasms in exposed groups of females.

Alveolar epithelial bronchiolization, an unusual nonneoplastic lesion, was also observed in the lungs of exposed male and female mice (Tables 20, C5, and D4). Microscopically, bronchiolization was characterized by extension of cuboidal epithelial cells from terminal bronchioles into adjacent alveolar ducts and alveoli (normally lined by squamous epithelium). This change was absent in controls, but the incidences and severities increased with increasing exposure concentration in males and females. Bronchiolization is considered a metaplastic change and not a precursor lesion to neoplasia. The absence of neoplastic or preneoplastic changes in all groups except 5,000 ppm males combined with high incidences of bronchiolization in these groups supports the lack of a relationship between bronchiolization and lung neoplasms.

*Liver:* The incidences of hepatocyte focal syncytial alteration were increased in all exposed groups of males (0 ppm, 2/50; 1,250 ppm, 13/50; 2,500 ppm, 17/50; 5,000 ppm, 33/50; Table C5). Syncytial alteration was generally a minimal change in all groups and consisted of a few scattered hepatocytes with multiple (typically four to six) nuclei and increased amounts of cytoplasm.

## Genetic Toxicology

*p*-Nitrotoluene (3.3 to 1,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without Aroclor-induced rat or hamster liver S9 (Table E1, Haworth *et al.*, 1983). A positive response was observed with *p*-nitrotoluene in the L5178Y mouse lymphoma cell assay in trials conducted with Aroclor 1254-induced male Fisher rat liver S9 (Table E2). In the mouse lymphoma assay with S9, test chemical precipitation was observed in all four trials. Using acetone as the solvent in the first three trials conducted with S9, a precipitate formed at concentrations of 300 µg/mL and greater. In the fourth trial, the solvent was changed to ethanol in an effort to reduce precipitation. However, precipitation again occurred in the fourth trial. Because significant increases in mutant fraction were noted at doses that did not produce test chemical precipitation, the test was judged to be positive in the presence of S9. Significantly increased numbers of sister chromatid exchanges were induced by *p*-nitrotoluene in cultured Chinese hamster ovary cells with and without S9 at doses that induced severe cell cycle delay, which is an indication of cytotoxicity (Table E3, Galloway *et al.*, 1987). Due to the observed levels of cytotoxicity, it should be noted that indirect mechanisms such as increased BrdU incorporation or decreased DNA synthesis might have been involved in the increased levels of sister chromatid exchanges observed in these cells. *p*-Nitrotoluene also induced aberrations in cultured Chinese hamster ovary cells at the highest dose tested in each of two trials conducted with S9 (Table E4; Galloway *et al.*, 1987). As in the sister chromatid exchange test, the cytotoxicity of *p*-nitrotoluene, as evidenced by cell cycle delay, may be a factor in the interpretation of the positive Abs response; however, cytotoxicity was also evident in the absence of S9, and no increase in aberrations was observed under those conditions (Table E4). *p*-Nitrotoluene caused no increases in micronucleated polychromatic erythrocytes in the bone marrow of male rats (Table E5). In male mice, the results of the initial trial were considered positive, based on the responses seen at the two lowest doses; the trend test was not significant due to a downturn in the level of response at the highest dose of 600 mg/kg (Table E6). A second trial in mice failed to induce a significant increase in micronucleated polychromatic erythrocytes over the same dose range, and the results of the test were therefore concluded to be negative overall.

# DISCUSSION AND CONCLUSIONS

This NTP Technical Report continues the reporting of the comparative biologic effects of the nitrotoluene isomers. The results for the 2-year carcinogenicity studies of *p*-nitrotoluene in F344/N rats and B6C3F$_1$ mice are described here. The 2-year studies for *o*-nitrotoluene are reported in Technical Report 504 (NTP, 2002).

In the 2-year *p*-nitrotoluene studies, survival of control and exposed groups of rats and mice was generally similar. Mean body weights of 5,000 ppm male and 2,500 and 5,000 ppm female rats, and 5,000 ppm male and female mice were less than those of the controls during most of the study; mean body weights of 1,250 ppm females were less during the second year of the study.

In the 2-year study in rats, the incidence of adenoma or carcinoma (combined) of the clitoral gland in 2,500 ppm females was significantly greater than that in controls. The incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) generally exceeded the historical ranges in control female rats given NTP-2000 diet and, except for carcinomas, in untreated controls given NIH-07 diet for 2 years. There was no increase in the incidence of clitoral gland hyperplasia in any exposed group, and the incidence of adenoma or carcinoma (combined) in the 5,000 ppm group was not increased. Proliferative lesions (hyperplasia, adenoma, and carcinoma) of the clitoral gland are thought to represent a morphologic and biologic continuum. Compression and distortion of the acinar architecture generally distinguishes neoplasms from hyperplasia, with carcinomas being larger and having more irregular borders than adenomas. The significantly increased neoplasm incidence in 2,500 ppm females was considered some evidence of a carcinogenic effect because the incidences of clitoral gland adenoma and clitoral gland adenoma or carcinoma (combined) exceeded the historical control ranges for these neoplasms in rats fed either diet. Moreover, in a previous study of *p*-nitrobenzoic acid, a major metabolite of *p*-nitrotoluene, an increased incidence of clitoral gland neoplasms also occurred (Table 21; NTP, 1994).

The absence of an increased incidence of clitoral gland neoplasms in 5,000 ppm females may have been related to lower body weights in this group (the final mean body weight of 5,000 ppm females was 71% that of controls). In an NTP study of dietary restriction (Haseman, 1998), the incidence of clitoral gland neoplasms in feed-restricted controls was 6.1%, while the incidence of clitoral gland neoplasms in concurrent *ad libitum*-fed controls was 14.3%. The final mean body weights of the feed-restricted female rats was 87% that of controls (NTP, 1997). A similar reduction in the incidences of clitoral gland neoplasms (4.4% versus 10.2%) was seen in larger groups of controls from the broader NTP database that had been weight-matched to the feed-restricted controls compared to animals weight-matched to the much heavier *ad libitum*-fed controls from the dietary restriction study (Abdo and Kari, 1996; NTP, 1997; Haseman, 1998). These results imply that reduced body weight may be associated with decreased incidences of clitoral gland neoplasms, and the apparent downturn in the incidences of these neoplasms in 5,000 ppm female rats in the current study may have been due to reduced body weight.

The incidences of subcutaneous fibroma and of subcutaneous fibroma or fibrosarcoma (combined) in 2,500 ppm males were significantly greater than those in controls and exceeded the ranges observed in both the NTP-2000 and NIH-07 historical control databases. Fibromas were identified grossly at necropsy as large masses in the subcutis and, microscopically, were composed of scattered spindle cells separated by abundant collagenous matrix.

The significant increases in subcutaneous neoplasm incidences in 2,500 ppm males is suggestive of a chemical-related effect. However, there is no supporting increased neoplasm incidence in 5,000 ppm males. Although body weights of 5,000 ppm males were slightly less than those of the controls throughout the study, subcutaneous neoplasms are not known to be sensitive to body weight reduction. Therefore, the increased incidences of subcutaneous neoplasms in 2,500 ppm males were considered an uncertain finding.

In the 13-week feed studies (NTP, 1992), there was evidence that *p*-nitrotoluene induced $\alpha$2u-globulin nephropathy in male rats. This evidence included increased incidences and/or severities of hyaline droplets within the proximal renal tubule epithelium and the positive ELISA. The ELISA results indicated some of the protein (hyaline droplets) was $\alpha$2u-globulin, the

**TABLE 21**
**Comparison of Body Weights and Selected Neoplasms and Nonneoplastic Lesions in F344/N Rats in the 2-Year Feed Studies of *p*-Nitrotoluene and *p*-Nitrobenzoic Acid**

| | *p*-Nitrotoluene | | | | *p*-Nitrobenzoic Acid[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
| **Male** | | | | | | | | |
| Dose (mg/kg) | 0 | 55 | 110 | 240 | 0 | 50 | 100 | 210 |
| Mean body weight for year 2 of the study (% of controls) | | 99 | 98 | 89 | | 101 | 101 | 98 |
| Mononuclear cell leukemia[b] | 24/50 (48%) | 12/50 (24%) | 5/50 (10%) | 4/50 (8%) | 29/50 (58%) | 35/50 (70%) | 26/50 (52%) | 2/50 (4%) |
| **Female** | | | | | | | | |
| Dose (mg/kg) | 0 | 60 | 125 | 265 | 0 | 60 | 125 | 250 |
| Mean body weight for year 2 of the study (% of controls) | | 93 | 90 | 75 | | 97 | 93 | 86 |
| Clitoral gland, adenoma or carcinoma | 8/50 (16%) | 12/50 (24%) | 20/50 (40%) | 8/49 (16%) | 4/50 (8%) | 14/49 (29%) | 15/49 (31%) | 15/50 (30%) |
| Mononuclear cell leukemia | 13/50 (26%) | 12/50 (24%) | 3/50 (6%) | 1/50 (2%) | 17/50 (34%) | 11/50 (22%) | 3/50 (6%) | 0/50 (0%) |
| Mammary gland, fibroadenoma, adenoma, or carcinoma | 14/50 (28%) | 17/50 (34%) | 20/50 (40%) | 5/50 (10%) | 25/50 (50%) | 24/50 (48%) | 28/50 (56%) | 26/50 (52%) |

[a] NTP, 1994
[b] Data presented as number of animals with lesion/number of animals necropsied (mononuclear cell leukemia and mammary gland) or number with tissue examined microscopically (clitoral gland)

proportion of which was increased in exposed groups. However, other renal changes normally associated with α2u-globulin nephropathy were not observed, including granular casts and exacerbated chronic glomerular nephropathy. Therefore, *p*-nitrotoluene does not appear to be a strong inducer of α2u-globulin nephropathy. This weaker induction may explain the lack, in the current study, of increased incidences of renal neoplasms that usually occur with chemicals that induce α2u-globulin nephropathy. Female rats produce little α2u-globulin, and male rats cease production of this protein by 18 months of age (USEPA, 1991). Because of the difference in α2u-globulin production and the slightly different appearance of the hyaline droplets observed in the kidneys of exposed male and female rats in the 2-year study and in the 13-week study, the hyaline droplets observed at the two time stages were not considered related.

In the current studies, there were increased incidences of mild hematopoietic cell proliferation and pigmentation in the spleen of exposed male and female rats and decreased incidences of mononuclear cell leukemia. Survival in the exposed male rat groups was higher than in the controls, possibly due to decreased incidences of mononuclear cell leukemia in these groups. Significantly increased incidences of various types of altered cell foci in the liver of males and females were associated with exposure.

Nitroaromatic chemicals that cause hematopoiesis and hemosiderin pigment accumulation in the spleen also may cause a decrease in the incidence of mononuclear cell leukemia (Elwell *et al.*, 1996). The spleen plays a critical role in the pathogenesis of mononuclear cell leukemia. Although the stem cell for mononuclear cell leukemia is considered to be a lymphocyte of bone marrow origin, the initial histologic evidence for proliferation and expansion of these neoplastic cells occurs in the spleen where the leukemia cells fill the sinusoids. Alteration of the splenic microenvironment can affect the development of mononuclear cell leukemia. The increase in splenic toxicity and decrease in the incidence of mononuclear cell leukemia in the current study are consistent with similar response patterns seen with other nitroaromatic compounds in the NTP series of studies in rats. However, the relationship between splenic toxicity and mononuclear cell leukemia has typically been seen with strong hematotoxic chemicals and usually with much more severe splenic changes than those seen with *p*-nitrotoluene. With *p*-nitrotoluene, only mild anemia was noted at 13 weeks (NTP, 1992). *p*-Nitrobenzoic acid induced anemia and increased methemoglobin concentrations at 13 weeks and caused a strikingly similar decrease in the incidence of mononuclear cell leukemia at 2 years, similar to that in the current study (Table 21; NTP, 1994).

The testicular degeneration observed in male rats in the 2-year study was consistent with degeneration observed at this site in the 13-week study. In the 2-year study, the combination of the increased incidence of interstitial cell hyperplasia in the 5,000 ppm group and the decreased incidence of interstitial cell adenoma may have been related to chemical exposure. Decreased incidences of interstitial cell neoplasms are unusual and not generally due to lower body weights in treated animals. In some studies (e.g., NTP, 1988, 1989) decreased incidences of interstitial cell neoplasms appeared related to chronic testicular toxicity, although a chemical effect on seminiferous tubules at 2 years is difficult to assess because atrophy can be due to aging or to interstitial cell neoplasms. The presence of moderate to severe atrophy at 2 years, as well as the presence of degeneration in the 13-week *p*-nitrotoluene study, would support a direct toxic effect.

The incidence of mammary gland fibroadenoma was decreased in 5,000 ppm female rats. The decreased incidence may be related to reduced body weight gain as observed in other studies (Seilkop, 1995; Haseman and Johnson, 1996; Haseman *et al*., 1997). The final mean body weight of 5,000 ppm female rats was 29% less than that of the controls. The 5,000 ppm female rats were quite small, attaining a maximum mean body weight of only 213 g (Table 8), one of the lowest maximum mean body weights ever reported in an NTP study. This low body weight likely had an impact on the incidences of several neoplasms. For example, because the association between body weight and incidence of mammary gland neoplasms has been well documented (Seilkop, 1995; Haseman and Johnson, 1996; Haseman *et al*., 1997), low body weight was likely a major contributing factor to the decreased incidence of mammary gland fibroadenoma in the current study.

The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 5,000 ppm male mice was significantly increased. Alveolar epithelial hyperplasia, adenoma, and carcinoma are thought to represent a

morphologic and biologic continuum in the mouse lung. While not statistically significant, the incidence of alveolar epithelial hyperplasia in male mice generally increased with increasing exposure concentration. While the incidence of adenoma or carcinoma (combined) in 5,000 ppm males was within the range of historical controls fed NTP-2000 diet, it exceeded the range in untreated controls from the larger NIH-07 historical database. The incidence in the concurrent control group was at the lower end of both the NTP-2000 and NIH-07 historical control ranges and below the average rates (27.1% and 24.8%) for those diets. The majority of chemicals tested by the NTP that cause lung neoplasms in mice tend to cause increased incidences in both male and female mice. Currently, of the 35 studies positive for pulmonary carcinogenicity in mice, 28 had evidence of carcinogenicity in males and females. The increased incidences of lung neoplasms in male mice may have been related to administration of *p*-nitrotoluene. Incidences of lung neoplasms were not increased in female mice in this study.

Male and female mice also showed a treatment-related increase in the incidence of alveolar epithelial bronchiolization in the lung. Microscopically, bronchiolization was characterized by extension of cuboidal epithelium from terminal bronchioles into the adjacent alveolar ducts and alveoli, which are normally lined by simple squamous epithelium. Because this lesion was found in all exposed groups of mice and the neoplasm response was only seen in 5,000 ppm male mice, this lesion was considered to be a metaplastic change rather than a preneoplastic lesion. Bronchiolization is rarely seen as a chemical-related response in the mouse lung. Bronchiolization in mice has previously been reported to be related to viral infection (Nettesheim and Szakal, 1972). However, no viral infection was noted in mice in these studies (Appendix J), and no incidences of bronchiolization occurred in either of the male or female control groups.

No chemical-related lesions were seen in mice in the 13-week *p*-nitrotoluene studies (NTP, 1992). However, in the current 2-year study in mice, the incidences of hepatocyte syncytial alteration in the liver were increased in all exposed groups of males. This change was not observed in female mice, and it was not considered to be preneoplastic.

During the 2-year studies, *p*-acetamidobenzoic acid and *p*-nitrobenzoic acid concentrations were measured in the urine of rats and mice at 2 weeks and at 3, 12, and 18 months (Appendix F). In rats, ratios of *p*-nitrobenzoic acid and *p*-acetamidobenzoic acid to creatinine were linearly related to exposure concentration at each time point and for each sex. In rats the metabolite-to-creatinine ratio was generally larger at 2 weeks than at the later times. At this age, the animals are about half their final weight, but food consumption is high. Thus, exposure is highest on a weight basis to the young animals. This fact is not as obvious from the metabolite data. There appear to be differences in metabolism between male and female rats; females excrete more *p*-acetamidobenzoic acid. The urinary concentrations of *p*-acetamidobenzoic acid and *p*-nitrobenzoic acid in mouse urine were often below the level of detection, and no detailed comparisons were attempted.

Metabolism studies on *p*-nitrotoluene have identified *p*-nitrobenzoic acid, *p*-acetamidobenzoic acid, *p*-nitrohippuric acid, and *p*-nitrobenzylmercapturic acid in the urine of rats (Chism *et al.*, 1984; Appendix K). In mice, the urinary metabolites identified were *p*-nitrohippuric acid, 2-methyl-5-nitrophenyl sulfate, 2-methyl-5-nitrophenyl glucuronide, *p*-nitrobenzoic acid, and *p*-acetamidobenzoic acid (Appendixes F and K). In the current studies of animals given a single gavage dose of 200 mg/kg, the major metabolite in the urine of rats was *p*-nitrobenzoic acid (36% to 45% of the administered dose) while in mice, *p*-nitrobenzoic acid was a minor metabolite (6% to 10% of the administered dose). Ring-hydroxylation was a major metabolic pathway in mice, and major urinary metabolites in mice were conjugates of 2-methyl-5-nitrophenol (glucuronide and sulfate, total of 30% of the administered dose).

In the 2-year bioassays of *o*- and *p*-nitrotoluene, the *ortho* isomer was more carcinogenic than the *para* isomer (Table 22). This finding was predicted from earlier studies showing that covalent binding of *o*-nitrotoluene to total rat hepatic macromolecules is 3.5 times higher than that of *m*- or *p*-nitrotoluene (Rickert *et al.*, 1984). *o*-Nitrotoluene also binds to male F344 rat hepatic DNA, but no binding could be detected for *m*- or *p*-nitrotoluene (Rickert *et al.*, 1984). Of the three isomers, only *o*-nitrotoluene induced DNA repair in the *in vivo-in vitro*

**TABLE 22**
**Comparison of Selected Neoplasms in the 2-Year Feed Studies of *p*-Nitrotoluene and *o*-Nitrotoluene**

| | *p*-Nitrotoluene | | | | *o*-Nitrotoluene[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm | 0 ppm | 625 ppm | 1,250 ppm | 2,000 ppm | 2,000 ppm (Stop-Exposure) | 5,000 ppm (Stop-Exposure) |
| **Male Rats** | | | | | | | | | | |
| Average Daily Dose (mg/kg) | 0 | 55 | 110 | 240 | 0 | 25 | 50 | 90 | 125 | 315 |
| Survival | 31/50 | 38/50 | 38/50 | 40/50 | 39/60 | 18/60 | 3/60 | 0/60 | 11/60 | 0/60 |
| Mesothelium | | | | | | | | | | |
| Malignant Mesothelioma[b] | 5/50 | 2/50 | 1/50 | 4/50 | 2/60 | 20/60 | 29/60 | 44/60 | 44/60 | 54/60 |
| Skin (Subcutaneous) | | | | | | | | | | |
| Lipoma | 0/50 | 0/50 | 0/50 | 0/50 | 0/60 | 4/60 | 13/60 | 13/60 | 10/60 | 12/60 |
| Fibroma | 1/50 | 2/50 | 7/50 | 1/50 | 5/60 | 46/60 | 52/60 | 59/60 | 45/60 | 52/60 |
| Fibrosarcoma | 0/50 | 0/50 | 2/50 | 0/50 | 0/60 | 7/60 | 17/60 | 20/60 | 8/60 | 12/60 |
| Fibroma or Fibrosarcoma | 1/50 | 2/50 | 9/50 | 1/50 | 5/60 | 47/60 | 55/60 | 59/60 | 47/60 | 53/60 |
| Mammary Gland | | | | | | | | | | |
| Fibroadenoma | 0/50 | 0/50 | 0/50 | 0/50 | 0/60 | 7/60 | 10/60 | 2/60 | 13/60 | 20/60 |
| Liver | | | | | | | | | | |
| Hepatocellular Adenoma | 0/50 | 0/50 | 0/50 | 0/50 | 2/60 | 3/60 | 3/60 | 7/60 | 3/60 | 4/60 |
| Hepatocellular Adenoma or Carcinoma | 1/50 | 0/50 | 0/50 | 0/50 | 3/60 | 3/60 | 3/60 | 8/60 | 3/60 | 6/60 |
| Cholangiocarcinoma | 0/50 | 0/50 | 0/50 | 0/50 | 0/60 | 0/60 | 0/60 | 0/60 | 0/60 | 3/60 |
| Hepatocholangiocarcinoma | 0/50 | 0/50 | 0/50 | 0/50 | 0/60 | 1/60 | 0/60 | 1/60 | 0/60 | 0/60 |
| Lung | | | | | | | | | | |
| Alveolar/bronchiolar Adenoma | 1/50 | 0/50 | 2/50 | 2/50 | 1/60 | 5/60 | 1/60 | 2/60 | 3/60 | 8/60 |
| Alveolar/bronchiolar Adenoma or Carcinoma | 1/50 | 1/50 | 2/50 | 3/50 | 2/60 | 5/60 | 1/60 | 2/60 | 3/60 | 11/60 |

[a] NTP, 2002
[b] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.

**TABLE 22**
**Comparison of Selected Neoplasms in the 2-Year Feed Studies of *p*-Nitrotoluene and *o*-Nitrotoluene**

| | *p*-Nitrotoluene | | | | *o*-Nitrotoluene | | | |
|---|---|---|---|---|---|---|---|---|
| | **0 ppm** | **1,250 ppm** | **2,500 ppm** | **5,000 ppm** | **0 ppm** | **625 ppm** | **1,250 ppm** | **2,000 ppm** |
| **Female Rats** | | | | | | | | |
| Average Daily Dose (mg/kg) | 0 | 60 | 125 | 265 | 0 | 30 | 60 | 100 |
| Survival | 39/50 | 37/50 | 39/50 | 41/50 | 47/60 | 47/60 | 39/60 | 33/60 |
| Skin (Subcutaneous) | | | | | | | | |
| Fibroma | 0/50 | 0/50 | 0/50 | 1/49 | 3/59 | 3/60 | 18/60 | 19/60 |
| Fibroma or Fibrosarcoma | 1/50 | 1/50 | 0/50 | 2/50 | 3/60 | 3/60 | 21/60 | 22/60 |
| Mammary Gland | | | | | | | | |
| Fibroadenoma | 14/50 | 17/50 | 20/50 | 5/50 | 23/60 | 47/60 | 52/60 | 56/60 |
| Liver | | | | | | | | |
| Hepatocellular Adenoma | 0/50 | 0/50 | 1/50 | 0/50 | 1/60 | 0/59 | 1/60 | 6/60 |
| Clitoral Gland | | | | | | | | |
| Adenoma or Carcinoma | 8/50 | 12/50 | 20/50 | 8/49 | 14/59 | 13/57 | 6/54 | 3/53 |
| | **0 ppm** | **1,250 ppm** | **2,500 ppm** | **5,000 ppm** | **0 ppm** | **1,250 ppm** | **2,500 ppm** | **5,000 ppm** |
| **Male Mice** | | | | | | | | |
| Average Daily Dose (mg/kg) | 0 | 170 | 345 | 690 | 0 | 165 | 360 | 700 |
| Survival | 46/50 | 46/50 | 45/50 | 42/50 | 52/60 | 34/60 | 0/60 | 0/60 |
| Circulatory System | | | | | | | | |
| Hemangiosarcoma | 1/50 | 1/50 | 3/50 | 2/50 | 4/60 | 17/60 | 55/60 | 60/60 |
| Large Intestine (Cecum) | | | | | | | | |
| Carcinoma | 1/50 | 0/50 | 0/50 | 0/50 | 0/60 | 12/60 | 9/60 | 0/60 |
| Lung | | | | | | | | |
| Alveolar/bronchiolar Adenoma or Carcinoma | 8/50 | 14/50 | 12/50 | 19/50 | 14/60 | 7/60 | 6/60 | 0/60 |

**TABLE 22**
**Comparison of Selected Neoplasms in the 2-Year Feed Studies of *p*-Nitrotoluene and *o*-Nitrotoluene**

| | *p*-Nitrotoluene | | | | *o*-Nitrotoluene | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
| **Female Mice** | | | | | | | | |
| Average Daily Dose (mg/kg) | 0 | 155 | 315 | 660 | 0 | 150 | 320 | 710 |
| Survival | 46/50 | 47/50 | 43/50 | 49/50 | 52/60 | 46/60 | 47/60 | 5/60 |
| Circulatory System | | | | | | | | |
| Hemangiosarcoma | 1/50 | 1/50 | 0/50 | 1/50 | 0/60 | 2/60 | 3/60 | 50/60 |
| Large Intestine (Cecum) | | | | | | | | |
| Carcinoma | 0/50 | 0/50 | 0/50 | 0/50 | 0/60 | 1/60 | 4/60 | 3/60 |
| Liver | | | | | | | | |
| Hepatocellular Adenoma | 6/49 | 3/50 | 2/50 | 5/50 | 7/60 | 5/59 | 19/59 | 29/60 |
| Hepatocellular Carcinoma | 3/49 | 4/50 | 0/50 | 1/50 | 2/60 | 4/59 | 6/59 | 16/60 |
| Hepatocellular Adenoma or Carcinoma | 8/49 | 6/50 | 2/50 | 6/50 | 9/60 | 9/59 | 24/59 | 39/60 |

hepatocyte unscheduled DNA synthesis assay; the induction was seen in male F344 rats but not in female F344 rats (Doolittle *et al.*, 1983).

Quantitative differences in the metabolism of the mononitrotoluene isomers are a result of differences in the hepatic conjugation and oxidation of the first metabolic intermediates in rats, the mononitrobenzyl alcohols. The *o*-nitrotoluene metabolite 2-nitrobenzyl alcohol is the best substrate for microsomal glucuronyltransferase, and is thought to proceed through this pathway to form the ultimate carcinogen (Rickert *et al.*, 1984, 1985, 1986).

Upon metabolic activation, aromatic amine carcinogens yield electrophilic intermediates that bind to DNA, yielding N-(deoxyguanosin-8-yl)-arylamines (Marques *et al.*, 1997). *In vitro* DNA binding studies have suggested that while *o*-, *m*-, and *p*-substituted arylamines all bind to DNA, the substitution in the *ortho* position yields a more stable DNA adduct (Marques *et al.*, 1997), which is consistent with the greater potency of *o*-nitrotoluene as a carcinogen than *p*-nitrotoluene.

## CONCLUSIONS

Under the conditions of these 2-year feed studies there was *equivocal evidence of carcinogenic activity** of *p*-nitrotoluene in male F344/N rats based on increased incidences of subcutaneous skin neoplasms. There was *some evidence of carcinogenic activity* of *p*-nitrotoluene in female F344/N rats based on increased incidences of clitoral gland neoplasms. There was *equivocal evidence of carcinogenic activity* of *p*-nitrotoluene in male $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *no evidence of carcinogenic activity* of *p*-nitrotoluene in female $B6C3F_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

Exposure to *p*-nitrotoluene caused increased incidences of nonneoplastic lesions of the kidney, spleen, and liver in male and female rats, testis in male rats, and lung in male and female mice.

Decreased incidences of mononuclear cell leukemia in male and female rats and testicular interstitial cell adenoma in male rats were attributed to exposure to *p*-nitrotoluene.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

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# APPENDIX A
# SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF *p*-NITROTOLUENE

**TABLE A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 18 | 8 | 10 | 7 |
| Natural deaths | 1 | 4 | 2 | 3 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 30 | 38 | 38 | 40 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Intestine large, colon | (50) | (49) | (48) | (49) |
| Polyp adenomatous | | | 1 (2%) | |
| Intestine large, cecum | (49) | (50) | (50) | (50) |
| Intestine small, duodenum | (49) | (50) | (50) | (50) |
| Intestine small, ileum | (49) | (49) | (47) | (49) |
| Liver | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | 1 (2%) | | | |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | |
| Hepatocellular carcinoma | 1 (2%) | | | |
| Mesentery | (6) | (18) | (7) | (10) |
| Carcinoma, metastatic, thyroid gland | | | 1 (14%) | |
| Oral mucosa | | (1) | (1) | |
| Squamous cell carcinoma | | 1 (100%) | | |
| Squamous cell papilloma | | | 1 (100%) | |
| Pancreas | (50) | (50) | (49) | (50) |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | |
| Acinus, adenoma | | | 1 (2%) | |
| Acinus, carcinoma | 1 (2%) | | | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Schwannoma malignant | 1 (2%) | | | 1 (2%) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | | | | 1 (2%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Tongue | | (1) | | |
| Squamous cell carcinoma | | 1 (100%) | | |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | 1 (2%) |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Adenoma | | | 1 (2%) | 1 (2%) |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | |
| Bilateral, adenoma | | | | 1 (2%) |

**TABLE A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Endocrine System** (continued) | | | | |
| Adrenal medulla | (50) | (49) | (50) | (50) |
| Pheochromocytoma malignant | | 1 (2%) | | 1 (2%) |
| Pheochromocytoma benign | 3 (6%) | 3 (6%) | 2 (4%) | 4 (8%) |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Adenoma | 3 (6%) | | 1 (2%) | |
| Carcinoma | 2 (4%) | | | |
| Pituitary gland | (48) | (47) | (49) | (45) |
| Pars distalis, adenoma | 15 (31%) | 16 (34%) | 15 (31%) | 14 (31%) |
| Pars distalis, carcinoma | 1 (2%) | | | |
| Pars intermedia, adenoma | | | | 1 (2%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| C-cell, adenoma | 11 (22%) | 7 (14%) | 5 (10%) | 4 (8%) |
| C-cell, carcinoma | | | 1 (2%) | 2 (4%) |
| Follicular cell, adenoma | | | | 1 (2%) |
| Follicular cell, carcinoma | | 2 (4%) | 2 (4%) | |
| **General Body System** | | | | |
| Peritoneum | (6) | (2) | (1) | (5) |
| **Genital System** | | | | |
| Preputial gland | (50) | (49) | (50) | (50) |
| Adenoma | 2 (4%) | 4 (8%) | 1 (2%) | 5 (10%) |
| Carcinoma | 2 (4%) | 4 (8%) | 4 (8%) | 3 (6%) |
| Schwannoma malignant | 1 (2%) | | | |
| Prostate | (50) | (50) | (50) | (50) |
| Adenoma | 2 (4%) | 2 (4%) | 2 (4%) | |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Testes | (50) | (50) | (50) | (50) |
| Bilateral, interstitial cell, adenoma | 40 (80%) | 32 (64%) | 39 (78%) | 17 (34%) |
| Interstitial cell, adenoma | 9 (18%) | 14 (28%) | 6 (12%) | 17 (34%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Lymph node | (14) | (7) | (7) | (5) |
| Lymph node, mandibular | (48) | (49) | (49) | (49) |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | 1 (2%) |
| Lymph node, mesenteric | (50) | (50) | (50) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | |
| Thymus | (49) | (47) | (44) | (46) |
| Thymoma malignant | | | 1 (2%) | 2 (4%) |
| **Integumentary System** | | | | |
| Mammary gland | (45) | (48) | (43) | (36) |
| Fibroadenoma | | | 2 (5%) | |
| Skin | (50) | (50) | (50) | (50) |
| Basal cell adenoma | 1 (2%) | | 1 (2%) | 2 (4%) |
| Basal cell carcinoma | | 1 (2%) | | 1 (2%) |
| Carcinoma, metastatic, Zymbal's gland | 1 (2%) | | | |
| Fibrous histiocytoma | 1 (2%) | | | |
| Keratoacanthoma | 2 (4%) | 5 (10%) | 2 (4%) | |

**TABLE A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Integumentary System** (continued) | | | | |
| Skin (continued) | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | | 1 (2%) | 1 (2%) |
| Trichoepithelioma | | | 1 (2%) | |
| Sebaceous gland, adenoma | | 1 (2%) | | |
| Subcutaneous tissue, fibroma | 1 (2%) | 2 (4%) | 7 (14%) | 1 (2%) |
| Subcutaneous tissue, fibrosarcoma | | | 2 (4%) | |
| Subcutaneous tissue, hemangioma | 2 (4%) | | | |
| Subcutaneous tissue, schwannoma malignant | | 1 (2%) | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Osteosarcoma | | | | 1 (2%) |
| Skeletal muscle | (1) | (1) | (2) | (1) |
| Carcinoma, metastatic, pancreas | 1 (100%) | | | |
| Thymoma malignant, metastatic, thymus | | | | 1 (100%) |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma malignant | | 1 (2%) | | |
| Carcinoma, metastatic, pituitary gland | 1 (2%) | | | |
| Granular cell tumor malignant | 1 (2%) | | | |
| Spinal cord | (4) | (2) | (1) | (1) |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 1 (2%) | | 1 (2%) | 2 (4%) |
| Alveolar/bronchiolar adenoma, multiple | | | 1 (2%) | |
| Alveolar/bronchiolar carcinoma | | 1 (2%) | | 1 (2%) |
| Carcinoma, metastatic, pancreas | 1 (2%) | | | |
| Carcinoma, metastatic, preputial gland | | | 1 (2%) | |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | 1 (2%) |
| Thymoma malignant, metastatic, thymus | | | | 1 (2%) |
| **Special Senses System** | | | | |
| Eye | (3) | (2) | (1) | (1) |
| Melanoma malignant | 1 (33%) | | | |
| Zymbal's gland | (2) | | | (2) |
| Adenoma | | | | 1 (50%) |
| Carcinoma | 2 (100%) | | | 1 (50%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Urinary bladder | (50) | (50) | (50) | (50) |

**TABLE A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Leukemia mononuclear | 24 (48%) | 12 (24%) | 5 (10%) | 4 (8%) |
| Lymphoma malignant | 2 (4%) | | | 1 (2%) |
| Mesothelioma malignant | 5 (10%) | 2 (4%) | 1 (2%) | 4 (8%) |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | 50 | 50 | 48 | 46 |
| Total primary neoplasms | 140 | 113 | 107 | 95 |
| Total animals with benign neoplasms | 49 | 50 | 48 | 41 |
| Total benign neoplasms | 93 | 86 | 91 | 73 |
| Total animals with malignant neoplasms | 33 | 22 | 15 | 20 |
| Total malignant neoplasms | 47 | 27 | 16 | 22 |
| Total animals with metastatic neoplasms | 3 | | 3 | 4 |
| Total metastatic neoplasms | 5 | | 9 | 5 |

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

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

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

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

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 7 | 0 4 5 | 0 5 0 | 0 5 5 | 0 0 7 | 0 0 9 | 0 1 2 | 0 1 9 | 0 2 0 | 0 2 1 | 0 2 5 | 0 2 6 | 0 3 0 | 0 3 4 | 0 3 6 | 0 1 3 | 0 1 4 | 0 1 6 | 0 1 7 | 0 4 0 | 0 4 1 | 0 4 2 | 0 4 6 | 0 4 7 | 0 4 9 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | + | + | | | | | | | | | | | | | | | + | | | | 6 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Acinus, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | X | | | | | | | | | | | | X | | 3 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 3 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 2 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | 48 |
| Pars distalis, adenoma | X | | X | | X | | | | | X | | | X | | X | | | | X | | | | X | X | X | 15 |
| Pars distalis, carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | X | | | X | | X | | | | X | | | X | | X | | | | | | | | | | 11 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | + | + | | | | + | | | | | | | | | | + | | 6 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 3 7 8 | 5 0 4 | 5 9 1 | 5 9 2 | 6 0 9 | 6 2 7 | 6 3 7 | 6 3 9 | 6 3 9 | 6 7 9 | 6 8 1 | 6 8 7 | 6 9 5 | 7 0 4 | 7 1 3 | 7 2 2 | 7 2 2 | 7 2 6 | 7 2 6 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 1 5 | 0 3 9 | 0 2 2 | 0 3 1 | 0 1 0 | 0 1 8 | 0 1 1 | 0 0 6 | 0 3 5 | 0 0 8 | 0 2 9 | 0 2 7 | 0 0 4 | 0 2 8 | 0 2 4 | 0 3 8 | 0 4 8 | 0 4 3 | 0 4 4 | 0 0 1 | 0 0 2 | 0 0 3 | 0 2 3 | 0 3 2 | 0 3 3 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Schwannoma malignant | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | X | | X | X | X | X | X | X | | | X | | X | | X | X | X | X | X | X | X | X | X | X |
| Interstitial cell, adenoma | | | X | | | | | | | X | X | | X | | X | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | + | + | | | + | | | + | | + | | + | + | | | + | + | + | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, Zymbal's gland | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Subcutaneous tissue, hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | + | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Granular cell tumor malignant | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Peripheral nerve | | + | | + | | + | | | | | | | | | | | | | + | | | | | | |
| Spinal cord | | + | | + | | + | | | | | | | | | | | | | + | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 7 | 0 4 5 | 0 5 0 | 0 5 5 | 0 0 7 | 0 0 9 | 0 1 2 | 0 1 9 | 0 2 0 | 0 2 1 | 0 2 5 | 0 2 6 | 0 3 0 | 0 3 4 | 0 3 6 | 0 1 3 | 0 1 4 | 0 1 6 | 0 1 7 | 0 4 0 | 0 4 1 | 0 4 2 | 0 4 6 | 0 4 7 | 0 4 9 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | X | | | | | | | | | X | | | | | | | | | 2 |
| Carcinoma | | | | | | | | | | | X | | | | | | | | X | | | | | | | 2 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | | 2 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | X | X | X | X | X | X | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | | | 40 |
| Interstitial cell, adenoma | | | | | | | | X | | | X | | | | | | | | | | | | | X | X | 9 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | + | | | | | + | | | | | | | | | | | | + | | | | | + | | 14 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | 45 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Basal cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibrous histiocytoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| Squamous cell papilloma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, hemangioma | | | | X | | | | | | | | | | X | | | | | | | | | | | | 2 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Granular cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 3 7 8 | 5 0 4 | 5 9 1 | 5 9 2 | 6 0 9 | 6 2 7 | 6 3 7 | 6 3 9 | 6 3 9 | 6 7 9 | 6 8 1 | 6 8 7 | 6 9 5 | 7 0 4 | 7 1 3 | 7 2 2 | 7 2 2 | 7 2 6 | 7 2 6 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 1 5 | 0 3 9 | 0 2 2 | 0 3 1 | 0 1 0 | 0 1 8 | 0 1 1 | 0 1 6 | 0 3 5 | 0 3 8 | 0 2 9 | 0 2 7 | 0 2 4 | 0 2 8 | 0 2 4 | 0 3 8 | 0 4 8 | 0 4 3 | 0 4 4 | 0 4 4 | 0 0 1 | 0 0 2 | 0 0 3 | 0 2 3 | 0 3 2 | 0 3 3 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | + | | | | | | | |
| Melanoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | + | | | | | | | |
| Zymbal's gland | | | | | | | | | | | + | | | + | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | X | | | X | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | X | | X | | | | X | X | X | X | | X | X | X | X | X | | | | X | | X | |
| Lymphoma malignant | X | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Mesothelioma malignant | | X | | | X | | | | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 7 | 0 4 5 | 0 5 0 | 0 5 5 | 0 0 7 | 0 0 9 | 0 1 2 | 0 1 9 | 0 2 0 | 0 2 1 | 0 2 5 | 0 2 6 | 0 3 0 | 0 3 4 | 0 3 6 | 0 1 3 | 0 1 4 | 0 1 6 | 0 1 7 | 0 4 0 | 0 4 1 | 0 4 2 | 0 4 6 | 0 4 7 | 0 4 9 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | + | | | | | | | | | | | | | | | | | | | | + | 3 |
| Melanoma malignant | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | X | | X | X | X | | | X | | | | X | X | X | | | X | X | | | X | | | 24 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Mesothelioma malignant | | | | | | | | | X | X | | | | X | | | | | | | | | | | | 5 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 4 9 0 | 5 1 5 | 5 1 6 | 5 8 1 | 5 9 2 | 5 9 2 | 6 1 1 | 6 2 7 | 6 3 1 | 6 5 9 | 6 6 8 | 7 2 4 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 6 7 | 0 5 9 | 0 8 3 | 0 8 5 | 0 6 4 | 0 6 5 | 0 8 2 | 0 7 6 | 0 6 0 | 0 5 8 | 0 6 3 | 0 8 9 | 0 6 1 | 0 6 2 | 0 6 9 | 0 7 0 | 0 7 1 | 0 7 2 | 0 7 3 | 0 7 4 | 0 7 5 | 0 7 7 | 0 9 0 | 0 9 1 | 0 9 2 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | + | + | | | + | | | | + | + | | + | | + | | | + | | | + | | | + | + |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | + | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | I | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | M | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | X | | | | | | | X | | X | | | X | X | X | | | | | X | | | | X |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | X | | | X | | | | | | |
| Follicular cell, carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | + | | | | | | | | | | | | + | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | X | | |
| Carcinoma | | X | | | X | X | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | X | | | X | | X | X | X | | | | X | X | X | X | | X | X | X | X | | X | | X | X |
| Interstitial cell, adenoma | | | X | | X | | | | X | X | | | | | | | | | | | X | | X | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 0 9 3 | 0 0 9 4 | 0 0 9 5 | 0 0 5 1 | 0 0 5 2 | 0 0 5 3 | 0 0 5 7 | 0 0 6 6 | 0 0 6 8 | 0 0 7 8 | 0 0 7 9 | 0 0 8 0 | 0 0 8 4 | 0 0 8 6 | 0 0 9 9 | 0 1 0 0 | 0 0 5 4 | 0 0 5 5 | 0 0 5 6 | 0 0 8 1 | 0 0 8 7 | 0 0 8 8 | 0 0 9 6 | 0 0 9 7 | 0 0 9 8 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | + | + | + | + | | | | | + | + | | | | | | | | | | | + | | | 18 |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | + | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pheochromocytoma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | | | | | | X | | | | | X | | | | | | | X | | | | | | 3 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | 47 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Pars distalis, adenoma | | X | X | | | X | X | | | | | | X | X | | | | | | X | | X | | | | 16 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | X | | X | | | | X | | | | | | | | | X | X | | | | | | 7 |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | X | | | | | | X | | | | | | | | | | | | | | | 4 |
| Carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 4 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 2 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | X | | X | X | | X | X | | X | X | X | X | | X | X | X | X | X | | X | | X | | | 32 |
| Interstitial cell, adenoma | X | | X | | | | | | X | | | | | X | | | | | | X | | X | | X | X | 14 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 4 9 0 | 5 1 5 | 5 1 6 | 5 8 1 | 5 9 2 | 5 9 2 | 6 1 1 | 6 2 7 | 6 3 1 | 6 5 9 | 6 6 8 | 7 2 4 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 6 7 | 0 5 9 | 0 8 3 | 0 8 5 | 0 6 4 | 0 6 5 | 0 8 2 | 0 7 6 | 0 6 0 | 0 5 8 | 0 6 3 | 0 8 9 | 0 6 1 | 0 6 2 | 0 6 9 | 0 7 0 | 0 7 1 | 0 7 2 | 0 7 3 | 0 7 4 | 0 7 5 | 0 7 7 | 0 7 0 | 0 9 1 | 0 9 2 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | + | | | + | | | | | + | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | X | | | | X | | | | | | |
| Sebaceous gland, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, schwannoma malignant | X | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | + | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Peripheral nerve | | | | + | | | + | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | + | | | + | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lacrimal gland | | | | | | | | | | + | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | X | | X | X | X | | | | X | | | | X | | | | | | | | | |
| Mesothelioma malignant | | | | | | | | | | X | | | | | | | | | | | | | X | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 0 9 3 | 0 0 9 4 | 0 0 9 5 | 0 0 5 1 | 0 0 5 2 | 0 0 5 3 | 0 0 5 7 | 0 0 6 6 | 0 0 6 8 | 0 0 7 8 | 0 0 7 9 | 0 0 8 0 | 0 0 8 4 | 0 0 8 6 | 0 0 9 9 | 0 1 0 0 | 0 0 5 4 | 0 0 5 5 | 0 0 5 6 | 0 0 8 1 | 0 0 8 7 | 0 0 8 8 | 0 0 9 6 | 0 0 9 7 | 0 0 9 8 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | + | | | | | | | | | | + | | | | | | | | + | | + | | 7 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | M | + | + | + | + | + | + | 47 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Basal cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Keratoacanthoma | | | | | | | | | | | X | | | | | | | | | | | X | X | | | 5 |
| Sebaceous gland, adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | X | | | | | | | X | | | | | 2 |
| Subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar carcinoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | + | | | | | | + | | 2 |
| Lacrimal gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | X | | X | | | X | | | X | | | | | | X | | | | | | | | X | | 12 |
| Mesothelioma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 523 | 622 | 627 | 659 | 668 | 676 | 779 | 799 | 704 | 724 | 724 | 744 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 107 | 133 | 144 | 122 | 144 | 139 | 123 | 141 | 132 | 106 | 121 | 136 | 104 | 105 | 113 | 114 | 115 | 128 | 129 | 130 | 143 | 144 | 145 | 148 | 109 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | + | + | | | | | + | | | | | | | | | | | | | |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Parathyroid gland | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Pars distalis, adenoma | | | X | X | | | | | X | | | | | | | | X | | | | X | X | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | X | | | | | | | | | | X | | | | | |
| C-cell, carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | + | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 6 | 1 1 7 | 1 1 8 | 1 2 2 | 1 2 4 | 1 3 3 | 1 3 4 | 1 3 5 | 1 3 7 | 1 3 8 | 1 0 1 | 1 0 2 | 1 0 3 | 1 1 0 | 1 1 1 | 1 1 2 | 1 1 9 | 1 2 0 | 1 2 5 | 1 2 7 | 1 4 2 | 1 4 7 | 1 4 8 | 1 4 9 | 1 5 0 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | I | 48 |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | + | | | | | | | + | | | | | + | | | | | | | | | | + | | | 7 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Oral mucosa | | | + | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell papilloma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | X | | | | | | | | | | | | X | | | | | | | | | | 2 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pars distalis, adenoma | | | X | X | | | | X | X | X | X | | | | X | | | | | | X | X | | | | 15 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | X | | | | | | | | X | | | | | X | | | | | | | | | | 5 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Follicular cell, carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 523 | 621 | 627 | 659 | 668 | 676 | 679 | 679 | 704 | 724 | 724 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 10007 | 13101 | 14100 | 12606 | 14466 | 13639 | 12303 | 14101 | 13212 | 10606 | 12101 | 13616 | 10404 | 10505 | 11313 | 11414 | 11515 | 12808 | 12909 | 13010 | 14303 | 14404 | 14505 | 14608 | 10909 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | X | | | | | | | | | | | X | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | X | | | | X | | X | X | X | X | X | X | X | | | X | X | X | X | | | X | X | X |
| Interstitial cell, adenoma | | | | | X | | | | | | | | | | X | | | | | | X | X | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | + | | + | | + | | | | | | | | | | | | | | + |
| Lymph node, mandibular | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | M | + | + | M | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | + | M | + | M | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trichoepithelioma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | | | | X | | X | | | | | | | X | | | | | | | | | | X |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | X | | X | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | + | | | | | + | | | | | | | | | | | | | | | | | | |
| Mesothelioma malignant, metastatic, peritoneum | | | | | | | X | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 6 | 1 1 7 | 1 1 8 | 1 2 2 | 1 2 4 | 1 3 3 | 1 3 4 | 1 3 5 | 1 3 7 | 1 3 8 | 1 0 1 | 1 0 2 | 1 0 3 | 1 1 0 | 1 1 1 | 1 1 2 | 1 1 9 | 1 2 0 | 1 2 5 | 1 2 7 | 1 4 2 | 1 4 7 | 1 4 8 | 1 4 9 | 1 5 0 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | X | | | | | | | | X | | | | X | | | | | | | | | | | | | 4 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | X | X | X | | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | 39 |
| Interstitial cell, adenoma | | | | X | | | | | | X | | | | | | | | | | | | | | | | 6 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | + | | | | | | | | | | | | | | + | | | | | | | + | | | | 7 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | 44 |
| Thymoma malignant | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | 43 |
| Fibroadenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 2 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Basal cell adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 2 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Trichoepithelioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | | | | | | | | X | | | | | | | X | | | X | | | | | 7 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Mesothelioma malignant, metastatic, peritoneum | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 523 | 621 | 627 | 659 | 668 | 676 | 679 | 707 | 704 | 724 | 724 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 10007 | 10031 | 10040 | 10026 | 10046 | 10039 | 10023 | 10041 | 10032 | 10026 | 10021 | 10036 | 10044 | 10045 | 10113 | 10114 | 10115 | 10128 | 10229 | 10300 | 10343 | 10444 | 10445 | 10458 | 10509 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, thyroid gland | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urethra | | | | | | | | | | | | | | | + | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | X | | | | | | X | | | | | | | | | | X | | | | X |
| Mesothelioma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 6 | 1 1 7 | 1 1 8 | 1 2 2 | 1 2 4 | 1 3 3 | 1 3 4 | 1 3 5 | 1 3 7 | 1 3 8 | 1 0 1 | 1 0 2 | 1 0 3 | 1 1 0 | 1 1 1 | 1 1 2 | 1 1 9 | 1 2 0 | 1 2 5 | 1 2 7 | 1 4 2 | 1 4 7 | 1 4 8 | 1 4 9 | 1 5 0 | Total Tissues/ Tumors |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, preputial gland | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | + | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urethra | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | X | | | | | | | | | | | | | | | | | | | | | | 5 |
| Mesothelioma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

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

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 730 | 730 | 730 | 733 | 730 | 730 | 730 | 730 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 17 2 | 17 3 | 17 4 | 17 8 | 18 8 | 19 3 | 19 4 | 19 5 | 15 4 | 15 5 | 15 6 | 16 3 | 16 6 | 16 7 | 16 8 | 17 5 | 17 7 | 18 1 | 18 2 | 18 3 | 18 5 | 18 6 | 19 0 | 19 1 | 19 2 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | | + | | | + | | | + | | | | | | | + | | | | | | | | + | 10 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bilateral, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | X | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | 45 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | 45 |
| Pars distalis, adenoma | | | X | | X | | | | | X | | | | | | X | X | | | X | X | | X | X | | 14 |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | X | | | | | X | | | | | | | | | | | | X | | | | | 4 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | | | + | | + | | | | + | | | | | | | | 5 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 4 9 6 | 4 9 7 | 5 9 1 | 5 9 5 | 6 1 7 | 6 7 6 | 6 8 2 | 6 8 5 | 6 9 3 | 7 0 7 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 7 6 | 1 1 8 0 | 1 1 6 5 | 1 1 6 2 | 1 1 8 7 | 1 1 8 4 | 1 1 8 9 | 1 1 6 9 | 1 1 6 4 | 1 1 7 9 | 1 1 5 1 | 1 1 5 2 | 1 1 5 3 | 1 1 6 0 | 1 1 6 1 | 1 1 9 6 | 1 1 9 7 | 1 1 9 8 | 1 1 9 9 | 2 0 0 | 1 1 5 7 | 1 1 5 8 | 1 1 5 9 | 1 1 7 0 | 1 1 7 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | X | | | | X | | | | | X | | | |
| Carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | X | X | X | | | | X | | X | | X | X | | X | | X | X | X |
| Interstitial cell, adenoma | | | | | | | | | | | X | X | X | | | | | | | X | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | + | + | | | | | | | | | | | | | | | | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymoma malignant | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | M | + | + | + | + | + | + | + | + | + | + | M | + | + | M | M | + | + | M | + | + | M |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Basal cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skeletal muscle | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Thymoma malignant, metastatic, thymus | | X | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | + | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | + | | | | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 17702 | 17703 | 17704 | 17708 | 18808 | 19003 | 19004 | 19005 | 15404 | 15505 | 15606 | 16303 | 16606 | 16707 | 16808 | 17505 | 17707 | 18101 | 18202 | 18303 | 18505 | 18606 | 19004 | 19101 | 19202 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | X | X | | | | | | | | | | | | | | | 5 |
| Carcinoma | X | | | | | | | | | | | | | | | | | | | | X | | | | | 3 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | | | | | | | | X | | | | X | X | | | | | X | | X | | X | | | 17 |
| Interstitial cell, adenoma | | X | | X | X | X | X | | | X | | X | | | X | | X | X | | X | | X | | X | | 17 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | + | | | + | | | | | | | | | | | | | | 5 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | M | + | + | 46 |
| Thymoma malignant | | | | | | | | | | | | | | X | | | | | | | | | | | | 2 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | + | + | + | + | + | M | M | + | + | + | + | + | M | + | + | + | + | + | + | M | M | + | M | + | 36 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Basal cell adenoma | | | | | | X | | | | | | | | | | | | X | | | | | | | | 2 |
| Basal cell carcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Osteosarcoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymoma malignant, metastatic, thymus | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 4 9 6 | 4 9 7 | 5 9 1 | 5 9 5 | 6 1 7 | 6 7 6 | 6 8 2 | 6 8 5 | 6 9 3 | 7 0 7 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 7 6 | 1 1 8 0 | 1 1 6 5 | 1 1 6 2 | 1 1 8 7 | 1 1 8 4 | 1 1 8 9 | 1 1 6 9 | 1 1 6 4 | 1 1 7 9 | 1 1 5 1 | 1 1 5 2 | 1 1 5 3 | 1 1 6 0 | 1 1 6 1 | 1 1 9 6 | 1 1 9 7 | 1 1 9 8 | 1 1 9 9 | 1 1 9 0 | 2 0 0 0 | 1 1 5 7 | 1 1 5 8 | 1 1 5 9 | 1 1 7 0 | 1 1 7 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Thymoma malignant, metastatic, thymus | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | + | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | + | | | | | | | | | | | | | | | + | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | | | X | | X | | | | | | | | | | | | | | | | X |
| Lymphoma malignant | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Mesothelioma malignant | X | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 17 2 | 17 3 | 17 4 | 17 8 | 18 8 | 19 3 | 19 4 | 19 5 | 15 4 | 15 5 | 15 6 | 16 3 | 16 6 | 16 7 | 16 8 | 17 5 | 17 7 | 18 1 | 18 2 | 18 3 | 18 5 | 18 6 | 19 0 | 19 1 | 19 2 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | X | | | | | | | | | | X | | | | | | | | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymoma malignant, metastatic, thymus | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | | | | | | | | | | | | | | | | | X | | | | | | 4 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesothelioma malignant | | | | | | | | | | | | X | | X | | | | X | | | | | | | | 4 |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Adrenal Medulla: Benign Pheochromocytoma** | | | | |
| Overall rate[a] | 3/50 (6%) | 3/49 (6%) | 2/50 (4%) | 4/50 (8%) |
| Adjusted rate[b] | 6.7% | 6.8% | 4.2% | 8.6% |
| Terminal rate[c] | 2/31 (7%) | 3/37 (8%) | 2/38 (5%) | 3/40 (8%) |
| First incidence (days) | 681 | 729 (T) | 729 (T) | 707 |
| Poly-3 test[d] | P=0.445 | P=0.651 | P=0.477N | P=0.519 |
| **Adrenal Medulla: Benign or Malignant Pheochromocytoma** | | | | |
| Overall rate | 3/50 (6%) | 4/49 (8%) | 2/50 (4%) | 5/50 (10%) |
| Adjusted rate | 6.7% | 9.1% | 4.2% | 10.7% |
| Terminal rate | 2/31 (7%) | 4/37 (11%) | 2/38 (5%) | 4/40 (10%) |
| First incidence (days) | 681 | 729 (T) | 729 (T) | 707 |
| Poly-3 test | P=0.345 | P=0.487 | P=0.477N | P=0.376 |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 2.2% | 2.2% | 4.2% | 6.5% |
| Terminal rate | 0/31 (0%) | 1/38 (3%) | 2/38 (5%) | 3/40 (8%) |
| First incidence (days) | 504 | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.174 | P=0.758 | P=0.514 | P=0.313 |
| **Pancreatic Islets: Adenoma** | | | | |
| Overall rate | 3/50 (6%) | 0/50 (0%) | 1/49 (2%) | 0/50 (0%) |
| Adjusted rate | 6.7% | 0.0% | 2.2% | 0.0% |
| Terminal rate | 1/31 (3%) | 0/38 (0%) | 1/38 (3%) | 0/40 (0%) |
| First incidence (days) | 695 | —[e] | 729 (T) | — |
| Poly-3 test | P=0.082N | P=0.119N | P=0.293N | P=0.113N |
| **Pancreatic Islets: Adenoma or Carcinoma** | | | | |
| Overall rate | 5/50 (10%) | 0/50 (0%) | 1/49 (2%) | 0/50 (0%) |
| Adjusted rate | 11.1% | 0.0% | 2.2% | 0.0% |
| Terminal rate | 2/31 (7%) | 0/38 (0%) | 1/38 (3%) | 0/40 (0%) |
| First incidence (days) | 695 | — | 729 (T) | — |
| Poly-3 test | P=0.015N | P=0.031N | P=0.094N | P=0.028N |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | | |
| Overall rate | 15/48 (31%) | 16/47 (34%) | 15/49 (31%) | 14/45 (31%) |
| Adjusted rate | 34.2% | 36.3% | 31.8% | 33.0% |
| Terminal rate | 11/30 (37%) | 13/38 (34%) | 12/37 (32%) | 13/37 (35%) |
| First incidence (days) | 639 | 515 | 627 | 685 |
| Poly-3 test | P=0.454N | P=0.506 | P=0.495N | P=0.547N |
| **Pituitary Gland (Pars Distalis): Adenoma or Carcinoma** | | | | |
| Overall rate | 16/48 (33%) | 16/47 (34%) | 15/49 (31%) | 14/45 (31%) |
| Adjusted rate | 36.4% | 36.3% | 31.8% | 33.0% |
| Terminal rate | 12/30 (40%) | 13/38 (34%) | 12/37 (32%) | 13/37 (35%) |
| First incidence (days) | 639 | 515 | 627 | 685 |
| Poly-3 test | P=0.382N | P=0.582N | P=0.405N | P=0.458N |
| **Preputial Gland: Adenoma** | | | | |
| Overall rate | 2/50 (4%) | 4/49 (8%) | 1/50 (2%) | 5/50 (10%) |
| Adjusted rate | 4.5% | 8.8% | 2.1% | 10.8% |
| Terminal rate | 2/31 (7%) | 3/38 (8%) | 0/38 (0%) | 5/40 (13%) |
| First incidence (days) | 729 (T) | 490 | 679 | 729 (T) |
| Poly-3 test | P=0.227 | P=0.342 | P=0.479N | P=0.231 |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Preputial Gland: Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 4/49 (8%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted rate | 4.5% | 8.7% | 8.4% | 6.4% |
| Terminal rate | 2/31 (7%) | 1/38 (3%) | 4/38 (11%) | 2/40 (5%) |
| First incidence (days) | 729 (T) | 515 | 729 (T) | 676 |
| Poly-3 test | P=0.508 | P=0.351 | P=0.363 | P=0.519 |
| **Preputial Gland: Adenoma or Carcinoma** | | | | |
| Overall rate | 4/50 (8%) | 8/49 (16%) | 5/50 (10%) | 8/50 (16%) |
| Adjusted rate | 8.9% | 17.1% | 10.5% | 17.1% |
| Terminal rate | 4/31 (13%) | 4/38 (11%) | 4/38 (11%) | 7/40 (18%) |
| First incidence (days) | 729 (T) | 490 | 679 | 676 |
| Poly-3 test | P=0.249 | P=0.199 | P=0.537 | P=0.197 |
| **Skin: Keratoacanthoma** | | | | |
| Overall rate | 2/50 (4%) | 5/50 (10%) | 2/50 (4%) | 0/50 (0%) |
| Adjusted rate | 4.5% | 11.1% | 4.2% | 0.0% |
| Terminal rate | 2/31 (7%) | 5/38 (13%) | 2/38 (5%) | 0/40 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | — |
| Poly-3 test | P=0.082N | P=0.217 | P=0.674N | P=0.229N |
| **Skin: Squamous Cell Papilloma or Keratoacanthoma** | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 6.7% | 11.1% | 6.3% | 2.2% |
| Terminal rate | 3/31 (10%) | 5/38 (13%) | 3/38 (8%) | 1/40 (3%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.142N | P=0.357 | P=0.637N | P=0.292N |
| **Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma** | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 2.2% | 2.2% | 4.2% | 6.5% |
| Terminal rate | 0/31 (0%) | 0/38 (0%) | 2/38 (5%) | 3/40 (8%) |
| First incidence (days) | 637 | 627 | 729 (T) | 729 (T) |
| Poly-3 test | P=0.175 | P=0.760N | P=0.517 | P=0.316 |
| **Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma** | | | | |
| Overall rate | 4/50 (8%) | 6/50 (12%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted rate | 8.9% | 13.2% | 10.6% | 8.6% |
| Terminal rate | 3/31 (10%) | 5/38 (13%) | 5/38 (13%) | 4/40 (10%) |
| First incidence (days) | 637 | 627 | 729 (T) | 729 (T) |
| Poly-3 test | P=0.460N | P=0.371 | P=0.530 | P=0.627N |
| **Skin (Subcutaneous Tissue): Fibroma** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 7/50 (14%) | 1/50 (2%) |
| Adjusted rate | 2.2% | 4.5% | 14.7% | 2.1% |
| Terminal rate | 0/31 (0%) | 2/38 (5%) | 5/38 (13%) | 0/40 (0%) |
| First incidence (days) | 695 | 729 (T) | 676 | 591 |
| Poly-3 test | P=0.561 | P=0.500 | P=0.037 | P=0.751N |
| **Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 9/50 (18%) | 1/50 (2%) |
| Adjusted rate | 2.2% | 4.5% | 18.8% | 2.1% |
| Terminal rate | 0/31 (0%) | 2/38 (5%) | 5/38 (13%) | 0/40 (0%) |
| First incidence (days) | 695 | 729 (T) | 676 | 591 |
| Poly-3 test | P=0.525 | P=0.500 | P=0.011 | P=0.751N |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma** | | | | |
| Overall rate | 2/50 (4%) | 2/50 (4%) | 9/50 (18%) | 1/50 (2%) |
| Adjusted rate | 4.5% | 4.5% | 18.8% | 2.1% |
| Terminal rate | 1/31 (3%) | 2/38 (5%) | 5/38 (13%) | 0/40 (0%) |
| First incidence (days) | 695 | 729 (T) | 676 | 591 |
| Poly-3 test | P=0.497N | P=0.694 | P=0.032 | P=0.485N |
| **Testes: Adenoma** | | | | |
| Overall rate | 49/50 (98%) | 46/50 (92%) | 45/50 (90%) | 34/50 (68%) |
| Adjusted rate | 99.7% | 93.6% | 92.7% | 72.5% |
| Terminal rate | 31/31 (100%) | 36/38 (95%) | 37/38 (97%) | 31/40 (78%) |
| First incidence (days) | 504 | 490 | 621 | 685 |
| Poly-3 test | P<0.001N | P=0.110N | P=0.066N | P<0.001N |
| **Thyroid Gland (C-cell): Adenoma** | | | | |
| Overall rate | 11/50 (22%) | 7/50 (14%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted rate | 24.4% | 15.6% | 10.6% | 8.6% |
| Terminal rate | 7/31 (23%) | 7/38 (18%) | 4/38 (11%) | 4/40 (10%) |
| First incidence (days) | 704 | 729 (T) | 724 | 729 (T) |
| Poly-3 test | P=0.025N | P=0.216N | P=0.067N | P=0.037N |
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 11/50 (22%) | 7/50 (14%) | 6/50 (12%) | 6/50 (12%) |
| Adjusted rate | 24.4% | 15.6% | 12.6% | 12.9% |
| Terminal rate | 7/31 (23%) | 7/38 (18%) | 4/38 (11%) | 6/40 (15%) |
| First incidence (days) | 704 | 729 (T) | 676 | 729 (T) |
| Poly-3 test | P=0.110N | P=0.216N | P=0.114N | P=0.124N |
| **All Organs: Mononuclear Cell Leukemia** | | | | |
| Overall rate | 24/50 (48%) | 12/50 (24%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted rate | 51.6% | 25.7% | 10.5% | 8.6% |
| Terminal rate | 13/31 (42%) | 7/38 (18%) | 3/38 (8%) | 2/40 (5%) |
| First incidence (days) | 592 | 581 | 668 | 685 |
| Poly-3 test | P<0.001N | P=0.007N | P<0.001N | P<0.001N |
| **All Organs: Malignant Mesothelioma** | | | | |
| Overall rate | 5/50 (10%) | 2/50 (4%) | 1/50 (2%) | 4/50 (8%) |
| Adjusted rate | 10.9% | 4.4% | 2.1% | 8.5% |
| Terminal rate | 3/31 (10%) | 1/38 (3%) | 0/38 (0%) | 3/40 (8%) |
| First incidence (days) | 504 | 659 | 679 | 496 |
| Poly-3 test | P=0.485N | P=0.222N | P=0.094N | P=0.483N |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 49/50 (98%) | 50/50 (100%) | 48/50 (96%) | 41/50 (82%) |
| Adjusted rate | 99.7% | 100.0% | 97.2% | 86.5% |
| Terminal rate | 31/31 (100%) | 38/38 (100%) | 37/38 (97%) | 37/40 (93%) |
| First incidence (days) | 504 | 490 | 621 | 591 |
| Poly-3 test | P<0.001N | P=1.000 | P=0.416N | P=0.006N |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 33/50 (66%) | 22/50 (44%) | 15/50 (30%) | 20/50 (40%) |
| Adjusted rate | 66.4% | 44.5% | 31.1% | 41.1% |
| Terminal rate | 15/31 (48%) | 12/38 (32%) | 8/38 (21%) | 13/40 (33%) |
| First incidence (days) | 378 | 490 | 668 | 496 |
| Poly-3 test | P=0.009N | P=0.021N | P<0.001N | P=0.008N |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 50/50 (100%) | 50/50 (100%) | 48/50 (96%) | 46/50 (92%) |
| Adjusted rate | 100.0% | 100.0% | 97.2% | 93.6% |
| Terminal rate | 31/31 (100%) | 38/38 (100%) | 37/38 (97%) | 38/40 (95%) |
| First incidence (days) | 378 | 490 | 621 | 496 |
| Poly-3 test | P=0.011N | —[f] | P=0.361N | P=0.086N |

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

**TABLE A4a**
**Historical Incidence of Fibroma and Fibrosarcoma of the Skin (Subcutaneous) in Control Male F344/N Rats**

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Fibroma | Fibrosarcoma | Fibroma or Fibrosarcoma |
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | | | |
| Citral (feed) | 2/100 | 2/100 | 4/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 2/50 | 0/50 | 2/50 |
| Indium phosphide (inhalation) | 1/50 | 1/50 | 2/50 |
| 60-Hz Magnetic fields (whole body exposure) | 12/100 | 1/100 | 13/100 |
| Methacrylonitrile (gavage) | 3/50 | 0/50 | 3/50 |
| Naphthalene (inhalation) | 5/49 | 2/49 | 7/49 |
| *o*-Nitrotoluene (feed) | 5/60 | 0/60 | 5/60 |
| *p*-Nitrotoluene (feed) | 1/50 | 0/50 | 1/50 |
| Sodium nitrite (drinking water) | 0/50 | 1/50 | 1/50 |
| Vanadium pentoxide (inhalation) | 2/50 | 1/50 | 3/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | | | |
| Total (%) | 33/609 (5.4%) | 8/609 (1.3%) | 41/609 (6.7%) |
| Mean ± standard deviation | 5.1% ± 4.0% | 1.3% ±1.4% | 6.3% ± 4.2% |
| Range | 0%-12% | 0%-4% | 2%-14% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | | | |
| Benzyl acetate | 4/50 | 0/50 | 4/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 2/51 | 0/51 | 2/51 |
| Butyl benzyl phthalate | 5/50 | 0/50 | 5/50 |
| D&C Yellow No. 11 | 3/50 | 0/50 | 3/50 |
| Emodin | 1/50 | 0/50 | 1/50 |
| *o*-Nitroanisole | 1/50 | 0/50 | 1/50 |
| *p*-Nitrobenzoic acid | 4/50 | 1/50 | 5/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | | | |
| Total (%) | 56/1,004 (5.6%) | 9/1,004 (0.9%) | 65/1,004 (6.5%) |
| Mean ± standard deviation | 5.6% ± 3.2% | 0.9% ± 1.4% | 6.5% ± 3.1% |
| Range | 0%-10% | 0%-4% | 2%-10% |

[a] Data as of January 17, 2001
[b] Data as of December 21, 1999

**TABLE A4b**
**Historical Incidence of Mononuclear Cell Leukemia in Control Male F344/N Rats**

| Study | Incidence in Controls |
|---|---|
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | |
| Citral (feed) | 68/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 27/50 |
| Indium phosphide (inhalation) | 16/50 |
| 60-Hz Magnetic fields (whole body exposure) | 50/100 |
| Methacrylonitrile (gavage) | 20/50 |
| Naphthalene (inhalation) | 26/49 |
| *o*-Nitrotoluene (feed) | 30/60 |
| *p*-Nitrotoluene (feed) | 24/50 |
| Sodium nitrite (drinking water) | 17/50 |
| Vanadium pentoxide (inhalation) | 22/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | |
| Total (%) | 300/609 (49.3%) |
| Mean ± standard deviation | 47.3% ± 10.5% |
| Range | 32%-68% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | |
| Benzyl acetate | 16/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 27/51 |
| Butyl benzyl phthalate | 31/50 |
| D&C Yellow No. 11 | 37/50 |
| Emodin | 28/50 |
| *o*-Nitroanisole | 26/50 |
| *p*-Nitrobenzoic acid | 29/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | |
| Total (%) | 547/1,004 (54.5%) |
| Mean ± standard deviation | 54.5% ± 10.7% |
| Range | 32%-74% |

[a] Data as of January 17, 2001; includes data for lymphocytic, monocytic, and undifferentiated leukemia
[b] Data as of December 21, 1999; includes data for lymphocytic, monocytic, and undifferentiated leukemia

**TABLE A4c**
**Historical Incidence of Interstitial Cell Adenoma of the Testis in Control Male F344/N Rats**

| Study | Incidence in Controls |
|---|---|
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | |
| Citral (feed) | 96/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 41/50 |
| Indium phosphide (inhalation) | 40/50 |
| 60-Hz Magnetic fields (whole body exposure) | 93/100 |
| Methacrylonitrile (gavage) | 40/50 |
| Naphthalene (inhalation) | 38/49 |
| *o*-Nitrotoluene (feed) | 55/60 |
| *p*-Nitrotoluene (feed) | 49/50 |
| Sodium nitrite (drinking water) | 47/50 |
| Vanadium pentoxide (inhalation) | 36/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | |
| Total (%) | 535/609 (87.9%) |
| Mean ± standard deviation | 86.4% ± 9.1% |
| Range | 72%-98% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | |
| Benzyl acetate | 47/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 49/51 |
| Butyl benzyl phthalate | 44/50 |
| D&C Yellow No. 11 | 39/49 |
| Emodin | 41/50 |
| *o*-Nitroanisole | 48/50 |
| *p*-Nitrobenzoic acid | 44/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | |
| Total (%) | 889/1,003 (88.6%) |
| Mean ± standard deviation | 88.6% ± 6.0% |
| Range | 74%-96% |

[a] Data as of 17 January 2001
[b] Data as of 21 December 1999

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 18 | 8 | 10 | 7 |
| Natural deaths | 1 | 4 | 2 | 3 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 30 | 38 | 38 | 40 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Esophagus | (49) | (49) | (49) | (50) |
| Inflammation, chronic | | | | 1 (2%) |
| Intestine large, cecum | (49) | (50) | (50) | (50) |
| Edema | 1 (2%) | | | |
| Ulcer | 1 (2%) | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | | 1 (2%) | | 1 (2%) |
| Basophilic focus | 31 (62%) | 39 (78%) | 42 (84%) | 45 (90%) |
| Clear cell focus | 20 (40%) | 27 (54%) | 30 (60%) | 32 (64%) |
| Degeneration, cystic | | 3 (6%) | 5 (10%) | 1 (2%) |
| Eosinophilic focus | 5 (10%) | 5 (10%) | 5 (10%) | 19 (38%) |
| Hematopoietic cell proliferation | | 1 (2%) | | |
| Hemorrhage | 1 (2%) | | | 1 (2%) |
| Hepatodiaphragmatic nodule | 6 (12%) | 4 (8%) | 7 (14%) | 10 (20%) |
| Infiltration cellular, mixed cell | 3 (6%) | 2 (4%) | 4 (8%) | 2 (4%) |
| Mixed cell focus | 1 (2%) | 10 (20%) | 2 (4%) | 3 (6%) |
| Necrosis, focal | 2 (4%) | 1 (2%) | | |
| Thrombosis | | 1 (2%) | | |
| Bile duct, cyst | | | | 1 (2%) |
| Bile duct, hyperplasia | 45 (90%) | 44 (88%) | 42 (84%) | 42 (84%) |
| Centrilobular, necrosis | 2 (4%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Centrilobular, vacuolization cytoplasmic | | 1 (2%) | | |
| Hepatocyte, depletion glycogen, diffuse | | | | 1 (2%) |
| Hepatocyte, regeneration, focal | 1 (2%) | | | |
| Hepatocyte, vacuolization cytoplasmic | 3 (6%) | | 1 (2%) | 1 (2%) |
| Kupffer cell, pigmentation | 4 (8%) | | | 1 (2%) |
| Mesentery | (6) | (18) | (7) | (10) |
| Accessory spleen | 1 (17%) | | | 1 (10%) |
| Fat, necrosis | 4 (67%) | 18 (100%) | 7 (100%) | 9 (90%) |
| Pancreas | (50) | (50) | (49) | (50) |
| Atrophy | 12 (24%) | 18 (36%) | 16 (33%) | 7 (14%) |
| Acinus, hyperplasia, focal | 1 (2%) | 2 (4%) | 2 (4%) | 1 (2%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | | | 1 (2%) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Edema | 2 (4%) | 2 (4%) | 1 (2%) | |
| Ulcer | 4 (8%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Epithelium, hyperplasia | 2 (4%) | 2 (4%) | 3 (6%) | 2 (4%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Erosion | 5 (10%) | 1 (2%) | | 2 (4%) |
| Ulcer | 2 (4%) | | | 1 (2%) |
| Tooth | (1) | | | |
| Malformation | 1 (100%) | | | |

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

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 29 (58%) | 31 (62%) | 35 (70%) | 29 (58%) |
| Thrombosis | 1 (2%) | 1 (2%) | 1 (2%) | |
| Epicardium, hyperplasia | | | | 1 (2%) |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Accessory adrenal cortical nodule | 8 (16%) | 4 (8%) | 11 (22%) | 13 (26%) |
| Degeneration, fatty | 13 (26%) | 9 (18%) | 9 (18%) | 8 (16%) |
| Hyperplasia, diffuse | 1 (2%) | 1 (2%) | | |
| Hyperplasia, focal | | 3 (6%) | 1 (2%) | |
| Hypertrophy | 1 (2%) | | | |
| Hypertrophy, focal | 2 (4%) | 2 (4%) | 3 (6%) | 2 (4%) |
| Necrosis | 1 (2%) | | 1 (2%) | 1 (2%) |
| Adrenal medulla | (50) | (49) | (50) | (50) |
| Hyperplasia | 2 (4%) | 3 (6%) | 3 (6%) | 3 (6%) |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Hyperplasia | 2 (4%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Pituitary gland | (48) | (47) | (49) | (45) |
| Pars distalis, angiectasis | 1 (2%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Pars distalis, cyst | 4 (8%) | 8 (17%) | 7 (14%) | 8 (18%) |
| Pars distalis, hyperplasia, focal | 4 (8%) | 5 (11%) | 9 (18%) | 7 (16%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Ultimobranchial cyst | | | | 2 (4%) |
| C-cell, hyperplasia | 7 (14%) | 8 (16%) | 3 (6%) | 7 (14%) |
| Follicle, cyst | | 2 (4%) | 1 (2%) | |
| **General Body System** | | | | |
| Peritoneum | (6) | (2) | (1) | (5) |
| Inflammation, chronic | 1 (17%) | | | 1 (20%) |
| **Genital System** | | | | |
| Epididymis | (50) | (49) | (50) | (50) |
| Atypia cellular | 37 (74%) | 36 (73%) | 35 (70%) | 42 (84%) |
| Preputial gland | (50) | (49) | (50) | (50) |
| Hyperplasia | 1 (2%) | | | |
| Inflammation, chronic | 43 (86%) | 39 (80%) | 45 (90%) | 45 (90%) |
| Prostate | (50) | (50) | (50) | (50) |
| Corpora amylacea | | 1 (2%) | | |
| Inflammation, chronic | 27 (54%) | 29 (58%) | 24 (48%) | 18 (36%) |
| Epithelium, hyperplasia | 14 (28%) | 11 (22%) | 7 (14%) | 1 (2%) |
| Testes | (50) | (50) | (50) | (50) |
| Germinal epithelium, atrophy | 7 (14%) | 11 (22%) | 8 (16%) | 30 (60%) |
| Interstitial cell, hyperplasia | 8 (16%) | 15 (30%) | 7 (14%) | 23 (46%) |

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hyperplasia | 4 (8%) | 7 (14%) | 3 (6%) | 3 (6%) |
| Lymph node | (14) | (7) | (7) | (5) |
| Iliac, ectasia | | | 1 (14%) | |
| Iliac, hyperplasia, lymphoid | | | 1 (14%) | |
| Mediastinal, hemorrhage | 1 (7%) | 1 (14%) | 3 (43%) | 2 (40%) |
| Mediastinal, pigmentation | 7 (50%) | 3 (43%) | 5 (71%) | 3 (60%) |
| Pancreatic, hyperplasia, lymphoid | 1 (7%) | | | |
| Pancreatic, pigmentation | 2 (14%) | | 1 (14%) | 1 (20%) |
| Renal, hemorrhage | | | 1 (14%) | |
| Renal, hyperplasia, lymphoid | | | 1 (14%) | |
| Renal, pigmentation | 1 (7%) | | 2 (29%) | |
| Lymph node, mandibular | (48) | (49) | (49) | (49) |
| Ectasia | 5 (10%) | 2 (4%) | 2 (4%) | 4 (8%) |
| Hemorrhage | 3 (6%) | 4 (8%) | 3 (6%) | 4 (8%) |
| Hyperplasia, lymphoid | 4 (8%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Pigmentation | 19 (40%) | 14 (29%) | 30 (61%) | 26 (53%) |
| Lymph node, mesenteric | (50) | (50) | (50) | (50) |
| Hemorrhage | 4 (8%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Pigmentation | 3 (6%) | 3 (6%) | 1 (2%) | |
| Spleen | (50) | (50) | (50) | (50) |
| Accessory spleen | | | | 1 (2%) |
| Fibrosis | 3 (6%) | 4 (8%) | 2 (4%) | 4 (8%) |
| Hematopoietic cell proliferation | 9 (18%) | 13 (26%) | 19 (38%) | 25 (50%) |
| Hemorrhage | | 1 (2%) | 1 (2%) | 1 (2%) |
| Pigmentation | 10 (20%) | 12 (24%) | 24 (48%) | 38 (76%) |
| Thymus | (49) | (47) | (44) | (46) |
| Cyst | | | 2 (5%) | |
| **Integumentary System** | | | | |
| Mammary gland | (45) | (48) | (43) | (36) |
| Galactocele | 1 (2%) | | | |
| Hyperplasia | 29 (64%) | 22 (46%) | 27 (63%) | 26 (72%) |
| Inflammation, granulomatous | 1 (2%) | | | |
| Skin | (50) | (50) | (50) | (50) |
| Cyst epithelial inclusion | 2 (4%) | | | |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, chronic | | 1 (2%) | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Hyperostosis | 1 (2%) | | | |
| Cranium, osteopetrosis | 1 (2%) | | | |
| Femur, osteopetrosis | 2 (4%) | 1 (2%) | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Compression | 5 (10%) | 3 (6%) | 7 (14%) | 4 (8%) |
| Hydrocephalus | | 2 (4%) | 2 (4%) | 2 (4%) |
| Spinal cord | (4) | (2) | (1) | (1) |
| Cyst epithelial inclusion | | | | 1 (100%) |

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Hemorrhage | 5 (10%) | | 3 (6%) | |
| Infiltration cellular, histiocyte | 39 (78%) | 40 (80%) | 43 (86%) | 45 (90%) |
| Thrombosis | | 1 (2%) | | |
| Alveolar epithelium, hyperplasia | 3 (6%) | 2 (4%) | 5 (10%) | 4 (8%) |
| Nose | (50) | (50) | (50) | (50) |
| Foreign body | 5 (10%) | 6 (12%) | 9 (18%) | 1 (2%) |
| Inflammation, chronic | 7 (14%) | 8 (16%) | 8 (16%) | 3 (6%) |
| Respiratory epithelium, hyperplasia | 5 (10%) | 6 (12%) | 5 (10%) | |
| Respiratory epithelium, metaplasia, squamous | | 4 (8%) | 1 (2%) | |
| **Special Senses System** | | | | |
| Eye | (3) | (2) | (1) | (1) |
| Cataract | 1 (33%) | 2 (100%) | 1 (100%) | 1 (100%) |
| Hemorrhage | | 1 (50%) | | 1 (100%) |
| Retina, degeneration | | 2 (100%) | 1 (100%) | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Cyst | | | | 1 (2%) |
| Infarct | | 4 (8%) | 3 (6%) | 1 (2%) |
| Inflammation, chronic | 1 (2%) | 1 (2%) | | 1 (2%) |
| Nephropathy | 33 (66%) | 37 (74%) | 31 (62%) | 18 (36%) |
| Renal tubule, dilatation | 1 (2%) | | | 1 (2%) |
| Renal tubule, hyaline droplet | 2 (4%) | 23 (46%) | 27 (54%) | 18 (36%) |
| Renal tubule, hyperplasia | 1 (2%) | | | 1 (2%) |
| Renal tubule, hyperplasia, oncocytic | | | | 3 (6%) |
| Renal tubule, pigmentation | 10 (20%) | 28 (56%) | 47 (94%) | 46 (92%) |
| Transitional epithelium, hyperplasia | | 1 (2%) | | |

# APPENDIX B
# SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF *p*-NITROTOLUENE

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 7 | 12 | 10 | 7 |
| Natural deaths | 4 | 1 | 1 | 2 |
| Survivors | | | | |
| Terminal sacrifice | 39 | 37 | 39 | 41 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Intestine large, colon | (50) | (50) | (49) | (50) |
| Intestine large, cecum | (50) | (49) | (50) | (50) |
| Liver | (50) | (50) | (50) | (50) |
| Hepatocellular adenoma | | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Oral mucosa | (1) | | (1) | (1) |
| Squamous cell carcinoma | | | 1 (100%) | |
| Squamous cell papilloma | 1 (100%) | | | 1 (100%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Acinus, adenoma | | 1 (2%) | | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Tongue | (3) | (1) | | (1) |
| Squamous cell carcinoma | 1 (33%) | 1 (100%) | | 1 (100%) |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Endocardium, schwannoma malignant | 1 (2%) | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Adrenal medulla | (49) | (50) | (50) | (50) |
| Pheochromocytoma malignant | | 1 (2%) | 1 (2%) | |
| Pheochromocytoma benign | 2 (4%) | 1 (2%) | | 1 (2%) |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Pars distalis, adenoma | 15 (30%) | 23 (46%) | 17 (34%) | 11 (22%) |
| Pars intermedia, adenoma | | | 1 (2%) | 1 (2%) |
| Pars intermedia, carcinoma | | | | 1 (2%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Bilateral, C-cell, adenoma | | 1 (2%) | | |
| C-cell, adenoma | 6 (12%) | 2 (4%) | 9 (18%) | 2 (4%) |
| C-cell, carcinoma | | | 1 (2%) | 1 (2%) |
| Follicular cell, carcinoma | 1 (2%) | 1 (2%) | | 1 (2%) |
| **General Body System** | | | | |
| None | | | | |

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Genital System** | | | | |
| Clitoral gland | (50) | (50) | (50) | (49) |
| Adenoma | 7 (14%) | 8 (16%) | 13 (26%) | 6 (12%) |
| Adenoma, multiple | | | 2 (4%) | |
| Carcinoma | 2 (4%) | 4 (8%) | 6 (12%) | 1 (2%) |
| Carcinoma, multiple | | | | 1 (2%) |
| Ovary | (50) | (50) | (50) | (50) |
| Granulosa cell tumor malignant | | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Uterus | (50) | (50) | (50) | (50) |
| Carcinoma | | 1 (2%) | | |
| Fibroma | | 1 (2%) | | |
| Hemangioma | 1 (2%) | | | |
| Leiomyoma | | | | 1 (2%) |
| Polyp stromal | 6 (12%) | 4 (8%) | 10 (20%) | 8 (16%) |
| Polyp stromal, multiple | | | 1 (2%) | |
| Schwannoma malignant | 1 (2%) | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Lymph node | (4) | (8) | (3) | (11) |
| Lymph node, mandibular | (50) | (50) | (48) | (50) |
| Lymph node, mesenteric | (49) | (50) | (50) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Thymus | (48) | (48) | (45) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Carcinoma | 1 (2%) | | | |
| Fibroadenoma | 14 (28%) | 15 (30%) | 17 (34%) | 5 (10%) |
| Fibroadenoma, multiple | | 2 (4%) | 3 (6%) | |
| Skin | (50) | (50) | (50) | (49) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Trichoepithelioma | | | | 1 (2%) |
| Subcutaneous tissue, fibroma | | | | 1 (2%) |
| Subcutaneous tissue, fibrosarcoma | 1 (2%) | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, lipoma | 1 (2%) | | | |
| Subcutaneous tissue, sarcoma NOS | 1 (2%) | | | |
| **Musculoskeletal System** | | | | |
| None | | | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma malignant | 1 (2%) | 1 (2%) | | |
| Carcinoma, metastatic, pituitary gland | | | | 1 (2%) |
| Glioma malignant | | | | 1 (2%) |
| Oligodendroglioma malignant | | | 1 (2%) | |
| Spinal cord | (1) | (2) | | |

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | | | | 1 (2%) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Sarcoma NOS, metastatic, skin | 1 (2%) | | | |
| **Special Senses System** | | | | |
| Zymbal's gland | | | (1) | |
| Carcinoma | | | 1 (100%) | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Sarcoma | | | 1 (2%) | |
| Urinary bladder | (50) | (50) | (50) | (50) |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Leukemia mononuclear | 13 (26%) | 12 (24%) | 3 (6%) | 1 (2%) |
| Lymphoma malignant | | 1 (2%) | 1 (2%) | |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | 43 | 46 | 46 | 29 |
| Total primary neoplasms | 77 | 82 | 91 | 48 |
| Total animals with benign neoplasms | 33 | 39 | 41 | 27 |
| Total benign neoplasms | 53 | 58 | 74 | 39 |
| Total animals with malignant neoplasms | 22 | 22 | 16 | 7 |
| Total malignant neoplasms | 24 | 24 | 17 | 9 |
| Total animals with metastatic neoplasms | 1 | | | 1 |
| Total metastatic neoplasms | 1 | | | 1 |

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

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 3 8 0 | 4 9 7 | 5 0 4 | 5 7 4 | 5 9 1 | 6 5 5 | 6 7 6 | 6 9 3 | 6 9 5 | 7 0 8 | 7 1 2 | 7 2 9 | 7 3 0 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 3 0 | 2 1 3 | 2 1 8 | 2 0 5 | 2 3 2 | 2 0 9 | 2 4 8 | 2 2 1 | 2 0 8 | 2 3 9 | 2 3 5 | 2 4 9 | 2 0 3 | 2 0 1 | 2 0 2 | 2 0 4 | 2 3 6 | 2 3 7 | 2 3 8 | 2 4 0 | 2 1 1 | 2 1 2 | 2 1 4 | 2 1 5 | 2 1 6 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | | | | + | | | | | | | | | | | | | | | + | | | | | |
| Oral mucosa | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | + | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocardium, schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | X | X | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | M | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | X | | | | | | | X | | X | X | | | | | | X | X | | X | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | X | | | X | | X | | X | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Schwannoma malignant | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Vagina | | | | | | | | | M | | | | | | | | | | | + | | | | | |

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

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 1 7 | 2 1 9 | 2 2 0 | 2 3 1 | 2 3 3 | 2 3 4 | 2 4 1 | 2 4 2 | 2 4 3 | 2 4 4 | 2 4 5 | 2 4 6 | 2 4 7 | 2 5 0 | 2 0 6 | 2 0 7 | 2 1 0 | 2 2 2 | 2 2 3 | 2 2 4 | 2 2 5 | 2 2 6 | 2 2 7 | 2 2 8 | 2 2 9 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | 48 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | | | | | | | | | | | + | | | | | | | | | + | | | + | 5 |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | + | + | | | | | | | | | | | | | | | | 3 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endocardium, schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | | | | X | X | | | X | | | X | | | | X | | | X | | | | | | X | 15 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | X | | | | | | X | | | | | | | | | | | | | | | | | 6 |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | X | X | X | | X | | | | | X | | | X | | | | | | | | 7 |
| Carcinoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 2 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | X | | | | | X | | | | | X | | | | | | X | | | | | | X | | | 6 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 3 8 0 | 4 9 7 | 5 0 4 | 5 7 4 | 5 9 1 | 6 5 5 | 6 7 6 | 6 9 3 | 6 9 5 | 7 0 8 | 7 1 2 | 7 2 9 | 7 3 0 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 3 1 0 | 2 1 1 3 | 2 1 1 8 | 2 0 5 | 2 3 2 | 2 0 9 | 2 4 8 | 2 2 1 | 2 0 8 | 2 3 9 | 2 3 5 | 2 4 9 | 2 0 3 | 2 0 1 | 2 0 2 | 2 0 4 | 2 3 6 | 2 3 7 | 2 3 8 | 2 4 0 | 2 1 1 | 2 1 2 | 2 1 4 | 2 1 5 | 2 1 6 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | + | | | | | + | | | | | | + | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | X | | X | | | X | | X | | | | | X | | X | X | | X | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Subcutaneous tissue, lipoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma NOS, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | X | | | | | | | | X | X | | X | | | X | X | X | | | | | X | | X | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 1 7 | 2 1 9 | 2 2 0 | 2 3 1 | 2 3 3 | 2 3 4 | 2 4 1 | 2 4 2 | 2 4 3 | 2 4 4 | 2 4 5 | 2 4 6 | 2 4 7 | 2 5 0 | 2 0 6 | 2 0 7 | 2 1 0 | 2 2 2 | 2 2 3 | 2 2 4 | 2 2 5 | 2 2 6 | 2 2 7 | 2 2 8 | 2 2 9 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | + | | 4 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | 48 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Fibroadenoma | | | | | | | | X | X | | | | X | X | X | X | | | | | | | | | | 14 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, sarcoma NOS | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | 49 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma NOS, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | + | | | | | | | | | | | | | + | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | X | | | | | X | X | | | | | X | | | | | | | | | | | 13 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 3 8 7 | 5 2 8 | 5 7 7 | 6 2 9 | 6 3 9 | 6 3 9 | 6 5 9 | 6 7 5 | 7 0 1 | 7 0 2 | 7 2 4 | 7 2 4 | 7 2 8 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 2 9 1 | 2 9 3 | 2 9 0 | 2 6 2 | 2 9 4 | 2 8 2 | 2 5 8 | 2 7 4 | 2 6 3 | 2 7 8 | 2 9 9 | 2 6 7 | 2 5 1 | 2 5 2 | 2 5 3 | 2 5 4 | 2 5 5 | 2 6 1 | 2 6 4 | 2 6 5 | 2 7 1 | 2 7 2 | 2 7 3 | 2 7 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | A | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | + | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | + | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | X | X | X | | | | X | | | | | | | | | | | | | X | X | | X |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, C-cell, adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 5 6 | 2 5 7 | 2 5 9 | 2 6 0 | 2 8 6 | 2 8 7 | 2 8 8 | 2 8 9 | 2 9 6 | 2 9 7 | 2 9 8 | 3 0 0 | 2 6 6 | 2 6 8 | 2 6 9 | 2 7 0 | 2 7 6 | 2 7 7 | 2 7 9 | 2 8 0 | 2 8 1 | 2 8 4 | 2 8 5 | 2 9 2 | 2 9 5 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 48 |
| Intestine large, cecum | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | 47 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | + | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | | | | X | X | | X | X | X | X | X | X | | X | X | X | | X | | X | | X | X | | X | 23 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | | 2 |
| Follicular cell, carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 3 8 7 | 5 2 8 | 5 7 7 | 6 2 9 | 6 3 9 | 6 3 9 | 6 5 9 | 6 7 5 | 7 0 1 | 7 0 2 | 7 2 4 | 7 2 4 | 7 2 8 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 8 3 | 2 9 1 | 2 9 3 | 2 9 0 | 2 6 2 | 2 9 4 | 2 8 2 | 2 5 8 | 2 7 4 | 2 6 3 | 2 7 8 | 2 9 9 | 2 6 7 | 2 5 1 | 2 5 2 | 2 5 3 | 2 5 4 | 2 5 5 | 2 6 1 | 2 6 4 | 2 6 5 | 2 7 1 | 2 7 2 | 2 7 3 | 2 7 5 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | X | | | | | | | | X | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Fibroma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | X | | | | | | | | | | | X | | | | |
| Vagina | | | + | | | | | | | | + | + | | | | + | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Lymph node | + | | | | + | | | | + | | | + | | | | | | | | + | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | X | | | | X | | | X | X | X | | X | | | X | | |
| Fibroadenoma, multiple | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | + | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Peripheral nerve | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | + | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 5 5 6 | 2 5 5 7 | 2 5 5 9 | 2 6 6 0 | 2 8 8 6 | 2 8 8 7 | 2 8 8 8 | 2 8 8 9 | 2 9 0 6 | 2 9 0 7 | 2 9 0 8 | 3 0 0 0 | 2 6 6 6 | 2 6 6 8 | 2 6 6 9 | 2 7 0 0 | 2 7 7 6 | 2 7 7 7 | 2 7 7 9 | 2 8 0 0 | 2 8 8 1 | 2 8 8 4 | 2 8 8 5 | 2 9 2 2 | 2 9 2 5 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | X | | | | | | | | | X | | X | | | | | X | | X | X | | | 8 |
| Carcinoma | | | | | | X | | | | | X | | | X | | | | | X | | | | | | | 4 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | | X | | | | | | | | | | X | | | | 4 |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | + | | | + | | + | | | | | | | | | | | | | | | | | | | 8 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibroadenoma | | | X | X | X | X | | | | | | | | | | X | | | X | | | X | X | | | 15 |
| Fibroadenoma, multiple | | | | | | | | | | X | | | | | | | | | | | | | | | | 2 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 3 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 8 | 2 | 7 | 2 | 3 | 3 | 5 | 7 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 7 | 8 | 7 | 9 | 9 | 9 | 9 | 5 | 1 | 2 | 4 | 4 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 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 |
| | 8 | 9 | 9 | 9 | 6 | 9 | 8 | 5 | 7 | 6 | 7 | 9 | 6 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 7 | 7 | 7 | 7 |
| | 3 | 1 | 3 | 0 | 2 | 4 | 2 | 8 | 4 | 3 | 8 | 9 | 7 | 1 | 2 | 3 | 4 | 5 | 1 | 4 | 5 | 1 | 2 | 3 | 5 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Leukemia mononuclear | X | X | X | | | X | X | | X | X | | | | | | | | | | X | | | | | |
| Lymphoma malignant | | | | | | | | | | | | X | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| **Number of Days on Study** | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 5 6 | 2 5 7 | 2 5 9 | 2 6 0 | 2 8 6 | 2 8 7 | 2 8 8 | 2 8 9 | 2 9 6 | 2 9 7 | 2 9 8 | 3 0 0 | 2 6 6 | 2 6 8 | 2 6 9 | 2 7 0 | 2 7 6 | 2 7 7 | 2 7 9 | 2 8 0 | 2 8 1 | 2 8 4 | 2 8 5 | 2 9 2 | 2 9 5 | Total Tissues/ Tumors |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Leukemia mononuclear | X | | | | | | | | | | | X | | | | | | | X | | | | | | X | 12 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 3 8 7 | 6 3 3 | 6 3 9 | 6 5 5 | 6 7 5 | 6 7 6 | 6 7 6 | 6 7 6 | 6 7 6 | 6 7 9 | 6 8 7 | 7 2 1 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 9 | 3 4 8 | 3 3 7 | 3 1 8 | 3 4 6 | 3 0 4 | 3 3 3 | 3 3 4 | 3 4 9 | 3 3 5 | 3 0 1 | 3 0 2 | 3 0 3 | 3 0 5 | 3 1 6 | 3 1 7 | 3 1 9 | 3 2 0 | 3 2 1 | 3 2 2 | 3 2 3 | 3 2 4 | 3 2 5 | 3 2 6 | 3 2 7 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Intestine large, rectum | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | + | | | | | | |
| Oral mucosa | | | | | | | | | | | | + | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | X | X | X | | | | | | | | | | | | | | | X | X | | |
| Pars intermedia, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | X | | | | | | | | | X | | | | | | | X | X | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | X | | | | | | | | | | | | X | | X | | | | | | | | X | | X |
| Adenoma, multiple | | X | | | | | | | | | | | | | | | X | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | X | | | | X | X | | | X | | X | |
| Carcinoma, multiple | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | | | X | | | | | | | | | X | X | X | | | X | | | | | | X | |
| Polyp stromal, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Vagina | | | | | | | | | | | | | | | | | | | | | | + | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 2 8 | 3 2 9 | 3 3 0 | 3 1 1 | 3 1 2 | 3 1 3 | 3 1 4 | 3 1 5 | 3 3 1 | 3 3 2 | 3 4 1 | 3 4 2 | 4 4 3 | 4 4 4 | 4 4 5 | 3 0 6 | 3 0 7 | 3 0 8 | 3 0 9 | 3 1 0 | 3 3 6 | 3 3 8 | 3 4 0 | 4 4 7 | 3 5 0 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | + | | | | | | | | | | | | | | | | | | | + | | | | | | 3 |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | | X | X | | | X | X | | X | | | | X | X | | X | | | X | X | | | X | | 17 |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | X | X | | | | | X | | X | | | | | | | | | | | | X | | | | 9 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | X | | | X | | X | | | | | X | | | | X | | | | X | X | | | | 12 |
| Adenoma, multiple | | | | | | | | | | X | | | | | | | | | | | | | | | | 3 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Granulosa cell tumor malignant | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp stromal | | X | | | | X | X | | | | | | | | X | | | | | | | | | | | 10 |
| Polyp stromal, multiple | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 3 8 7 | 6 3 3 | 6 3 9 | 6 5 5 | 6 7 5 | 6 7 6 | 6 7 6 | 6 7 6 | 6 7 9 | 6 8 7 | 7 2 1 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 9 | 3 4 8 | 3 3 7 | 3 1 8 | 3 4 6 | 3 0 4 | 3 3 3 | 3 3 4 | 3 4 9 | 3 3 5 | 3 0 1 | 3 0 2 | 3 0 3 | 3 0 5 | 3 1 6 | 3 1 7 | 3 1 9 | 3 2 0 | 3 2 1 | 3 2 2 | 3 2 3 | 3 2 4 | 3 2 5 | 3 2 6 | 3 2 7 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | M | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | X | X | X | | X | | | | X | | X | | X | X | | X | | | | X | | |
| Fibroadenoma, multiple | | X | | | | | | | | | | | | | | | | | | X | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | + | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Oligodendroglioma malignant | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | + | | | | | | |
| Zymbal's gland | | | + | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | X | | | | X | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | X | | | | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 2 8 | 3 2 9 | 3 3 0 | 3 1 1 | 3 1 2 | 3 1 3 | 3 1 4 | 3 1 5 | 3 3 1 | 3 3 2 | 3 4 1 | 3 4 2 | 3 4 3 | 3 4 4 | 3 4 5 | 3 0 6 | 3 0 7 | 3 0 8 | 3 0 9 | 3 1 0 | 3 3 6 | 3 3 8 | 3 4 0 | 3 4 7 | 3 5 0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | + | | | | | | | | | | + | | | | | | | | | | 3 |
| Lymph node, mandibular | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | 45 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibroadenoma | | X | | | | X | | | X | | | X | | | | X | | | | X | X | | | | 17 |
| Fibroadenoma, multiple | | | | | | | | | | X | | | | | | | | | | | | | | | | 3 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Oligodendroglioma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | + | | | | + | | 3 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | | | | | | | | | | | | | | | | | | | | X | | | 3 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 5 3 2 | 6 1 7 | 6 3 9 | 6 7 2 | 6 7 6 | 6 9 0 | 7 2 2 | 7 2 5 | 7 2 8 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 7 7 | 3 5 5 | 3 7 3 | 3 6 4 | 3 5 8 | 3 6 3 | 3 7 6 | 3 8 1 | 3 6 9 | 3 9 1 | 3 9 2 | 3 9 3 | 3 9 4 | 3 9 5 | 3 5 1 | 3 5 2 | 3 5 3 | 3 5 4 | 3 5 6 | 3 5 7 | 3 5 9 | 3 6 0 | 3 7 8 | 3 7 9 | 3 8 0 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | I | + | I | + | + | + | + | I | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Oral mucosa | | | | | | | | | | | | | | | | | | + | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | X | | | | | | X | | | | | X | | | | | X | | X | | X | X | | |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars intermedia, carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | X | | | | | | X | | |
| Carcinoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | X | X | | | | | | | X | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 6 6 | 3 6 7 | 3 6 8 | 3 7 0 | 3 8 2 | 3 8 3 | 3 8 4 | 3 8 5 | 3 9 6 | 3 9 7 | 3 9 8 | 3 9 9 | 4 0 0 | 3 6 1 | 3 6 2 | 3 6 5 | 3 7 1 | 3 7 2 | 3 7 4 | 3 7 5 | 3 8 6 | 3 8 7 | 3 8 8 | 3 8 9 | 3 9 0 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | | X | X | | | | | X | | | X | | | | | | | | | | | | | | | 11 |
| Pars intermedia, adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Pars intermedia, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 2 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Follicular cell, carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | X | | | | | | | | | X | | | | | | X | X | | | | 6 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | X | X | | | | | | X | | | | X | | | | | | | | | | X | | | | 8 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 5 3 2 | 6 1 7 | 6 3 9 | 6 7 2 | 6 7 6 | 6 9 0 | 7 2 2 | 7 2 5 | 7 2 8 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 | 7 3 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 7 7 | 3 5 5 | 3 7 3 | 3 6 4 | 3 5 8 | 3 6 3 | 3 7 6 | 3 8 1 | 3 6 9 | 3 9 1 | 3 9 2 | 3 9 3 | 3 9 4 | 3 9 5 | 3 5 1 | 3 5 2 | 3 5 3 | 3 5 4 | 3 5 6 | 3 5 7 | 3 5 9 | 3 6 0 | 3 7 8 | 3 8 0 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | + | + | + | + | | | | | + | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | X | | | | | | | | | | X | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + |
| Trichoepithelioma | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | | | | | | | X | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | X | | | | | | | | | | | | | | | |
| Glioma malignant | | | | | | X | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | X | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | + | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 6 6 | 3 6 7 | 3 6 8 | 3 7 0 | 3 8 2 | 3 8 3 | 3 8 4 | 3 8 5 | 3 9 6 | 3 9 7 | 3 9 8 | 3 9 9 | 4 0 0 | 3 6 1 | 3 6 2 | 3 6 5 | 3 7 1 | 3 7 2 | 3 7 4 | 3 7 5 | 3 8 6 | 3 8 7 | 3 8 8 | 3 8 9 | 3 9 0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | + | + | | | | | | | | | | | + | | + | | | | + | | | | + | | | 11 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibroadenoma | | | | | | | | X | | | X | X | | | | | | | | | | | | | | 5 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Trichoepithelioma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Glioma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |

**TABLE B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Clitoral Gland: Adenoma** | | | | |
| Overall rate[a] | 7/50 (14%) | 8/50 (16%) | 15/50 (30%) | 6/49 (12%) |
| Adjusted rate[b] | 15.3% | 17.2% | 31.1% | 12.7% |
| Terminal rate[c] | 7/39 (18%) | 7/37 (19%) | 13/39 (33%) | 6/41 (15%) |
| First incidence (days) | 729 (T) | 701 | 387 | 729 (T) |
| Poly-3 test[d] | P=0.453N | P=0.509 | P=0.056 | P=0.475N |
| **Clitoral Gland: Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 4/50 (8%) | 6/50 (12%) | 2/49 (4%) |
| Adjusted rate | 4.4% | 8.6% | 12.7% | 4.2% |
| Terminal rate | 2/39 (5%) | 4/37 (11%) | 5/39 (13%) | 2/41 (5%) |
| First incidence (days) | 729 (T) | 729 (T) | 633 | 729 (T) |
| Poly-3 test | P=0.509N | P=0.341 | P=0.143 | P=0.682N |
| **Clitoral Gland: Adenoma or Carcinoma** | | | | |
| Overall rate | 8/50 (16%) | 12/50 (24%) | 20/50 (40%) | 8/49 (16%) |
| Adjusted rate | 17.4% | 25.9% | 41.5% | 16.9% |
| Terminal rate | 8/39 (21%) | 11/37 (30%) | 18/39 (46%) | 8/41 (20%) |
| First incidence (days) | 729 (T) | 701 | 387 | 729 (T) |
| Poly-3 test | P=0.487N | P=0.232 | P=0.008 | P=0.580N |
| **Mammary Gland: Fibroadenoma** | | | | |
| Overall rate | 14/50 (28%) | 17/50 (34%) | 20/50 (40%) | 5/50 (10%) |
| Adjusted rate | 30.2% | 36.6% | 41.5% | 10.4% |
| Terminal rate | 11/39 (28%) | 14/37 (38%) | 15/39 (39%) | 4/41 (10%) |
| First incidence (days) | 655 | 701 | 633 | 676 |
| Poly-3 test | P=0.008N | P=0.331 | P=0.176 | P=0.014N |
| **Mammary Gland: Fibroadenoma or Carcinoma** | | | | |
| Overall rate | 14/50 (28%) | 17/50 (34%) | 20/50 (40%) | 5/50 (10%) |
| Adjusted rate | 30.2% | 36.6% | 41.5% | 10.4% |
| Terminal rate | 11/39 (28%) | 14/37 (38%) | 15/39 (39%) | 4/41 (10%) |
| First incidence (days) | 655 | 701 | 633 | 676 |
| Poly-3 test | P=0.008N | P=0.331 | P=0.176 | P=0.014N |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | | |
| Overall rate | 15/50 (30%) | 23/50 (46%) | 17/50 (34%) | 11/50 (22%) |
| Adjusted rate | 32.2% | 48.3% | 35.7% | 22.6% |
| Terminal rate | 13/39 (33%) | 19/37 (51%) | 14/39 (36%) | 9/41 (22%) |
| First incidence (days) | 504 | 577 | 675 | 532 |
| Poly-3 test | P=0.057N | P=0.079 | P=0.442 | P=0.207N |
| **Thyroid Gland (C-cell): Adenoma** | | | | |
| Overall rate | 6/50 (12%) | 3/50 (6%) | 9/50 (18%) | 2/50 (4%) |
| Adjusted rate | 13.1% | 6.5% | 19.1% | 4.2% |
| Terminal rate | 6/39 (15%) | 3/37 (8%) | 8/39 (21%) | 2/41 (5%) |
| First incidence (days) | 729 (T) | 729 (T) | 676 | 729 (T) |
| Poly-3 test | P=0.183N | P=0.238N | P=0.307 | P=0.119N |
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 6/50 (12%) | 3/50 (6%) | 10/50 (20%) | 3/50 (6%) |
| Adjusted rate | 13.1% | 6.5% | 21.2% | 6.2% |
| Terminal rate | 6/39 (15%) | 3/37 (8%) | 9/39 (23%) | 3/41 (7%) |
| First incidence (days) | 729 (T) | 729 (T) | 676 | 729 (T) |
| Poly-3 test | P=0.312N | P=0.238N | P=0.223 | P=0.220N |

**TABLE B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Uterus: Stromal Polyp** | | | | |
| Overall rate | 6/50 (12%) | 4/50 (8%) | 11/50 (22%) | 8/50 (16%) |
| Adjusted rate | 13.1% | 8.6% | 23.3% | 16.6% |
| Terminal rate | 6/39 (15%) | 3/37 (8%) | 10/39 (26%) | 6/41 (15%) |
| First incidence (days) | 729 (T) | 702 | 655 | 690 |
| Poly-3 test | P=0.232 | P=0.363N | P=0.157 | P=0.425 |
| **All Organs: Mononuclear Cell Leukemia** | | | | |
| Overall rate | 13/50 (26%) | 12/50 (24%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 27.7% | 24.5% | 6.3% | 2.1% |
| Terminal rate | 10/39 (26%) | 5/37 (14%) | 1/39 (3%) | 1/41 (2%) |
| First incidence (days) | 380 | 387 | 676 | 729 (T) |
| Poly-3 test | P<0.001N | P=0.450N | P=0.005N | P<0.001N |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 33/50 (66%) | 39/50 (78%) | 41/50 (82%) | 27/50 (54%) |
| Adjusted rate | 70.0% | 81.7% | 82.9% | 55.1% |
| Terminal rate | 28/39 (72%) | 32/37 (87%) | 33/39 (85%) | 22/41 (54%) |
| First incidence (days) | 504 | 577 | 387 | 532 |
| Poly-3 test | P=0.018N | P=0.128 | P=0.098 | P=0.093N |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 22/50 (44%) | 22/50 (44%) | 16/50 (32%) | 7/50 (14%) |
| Adjusted rate | 46.1% | 44.3% | 33.0% | 14.5% |
| Terminal rate | 17/39 (44%) | 10/37 (27%) | 9/39 (23%) | 5/41 (12%) |
| First incidence (days) | 380 | 387 | 633 | 690 |
| Poly-3 test | P<0.001N | P=0.509N | P=0.133N | P<0.001N |
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 43/50 (86%) | 46/50 (92%) | 46/50 (92%) | 29/50 (58%) |
| Adjusted rate | 88.0% | 92.0% | 92.0% | 59.1% |
| Terminal rate | 34/39 (87%) | 33/37 (89%) | 35/39 (90%) | 24/41 (59%) |
| First incidence (days) | 380 | 387 | 387 | 532 |
| Poly-3 test | P<0.001N | P=0.371 | P=0.371 | P<0.001N |

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

**TABLE B4a**
**Historical Incidence of Clitoral Gland Neoplasms in Control Female F344/N Rats**

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | | | |
| Citral (feed) | 15/98 | 1/98 | 16/98 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 1/47 | 0/47 | 1/47 |
| Indium phosphide (inhalation) | 5/49 | 0/49 | 5/49 |
| 60-Hz Magnetic fields (whole body exposure) | 11/90 | 0/90 | 11/90 |
| Methacrylonitrile (gavage) | 2/49 | 1/49 | 3/49 |
| Naphthalene (inhalation) | 4/49 | 0/49 | 4/49 |
| *o*-Nitrotoluene (feed) | 12/59 | 2/59 | 14/59 |
| *p*-Nitrotoluene (feed) | 7/50 | 2/50 | 8/50 |
| Riddelliine (gavage) | 7/49 | 3/49 | 10/49 |
| Sodium nitrite (drinking water) | 8/46 | 2/46 | 10/46 |
| Vanadium pentoxide (inhalation) | 2/50 | 0/50 | 2/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | | | |
| Total (%) | 74/636 (11.6%) | 11/636 (1.7%) | 84/636 (13.2%) |
| Mean ± standard deviation | 11.1% ± 5.9% | 1.9% ± 2.2% | 12.8% ± 7.4% |
| Range | 2%-20% | 0%-6% | 2%-24% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | | | |
| Benzyl acetate | 0/50 | 1/50 | 1/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 4/48 | 1/48 | 5/48 |
| Butyl benzyl phthalate | 3/50 | 4/50 | 7/50 |
| D&C Yellow No. 11 | 11/49 | 6/49 | 17/49 |
| Emodin | 10/49 | 2/49 | 12/49 |
| *o*-Nitroanisole | 3/45 | 4/45 | 7/45 |
| *p*-Nitrobenzoic acid | 4/50 | 1/50 | 4/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | | | |
| Total (%) | 89/968 (9.2%) | 30/968 (3.1%) | 118/968 (12.2%) |
| Mean ± standard deviation | 9.2% ± 6.0% | 3.1% ± 3.2% | 12.2% ± 7.7% |
| Range | 0%-22% | 0%-12% | 2%-35% |

[a] Data as of January 17, 2001
[b] Data as of December 21, 1999

**TABLE B4b**
**Historical Incidence of Mononuclear Cell Leukemia in Control Female F344/N Rats**

| Study | Incidence in Controls |
|---|---|
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | |
| Citral (feed) | 24/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 8/50 |
| Indium phosphide (inhalation) | 14/50 |
| 60-Hz Magnetic fields (whole body exposure) | 20/100 |
| Methacrylonitrile (gavage) | 21/50 |
| Naphthalene (inhalation) | 16/49 |
| *o*-Nitrotoluene (feed) | 21/60 |
| *p*-Nitrotoluene (feed) | 13/50 |
| Riddelliine (gavage) | 12/50 |
| Sodium nitrite (drinking water) | 15/50 |
| Vanadium pentoxide (inhalation) | 21/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | |
| Total (%) | 185/659 (28.1%) |
| Mean ± standard deviation | 29.1% ± 8.4% |
| Range | 16%-42% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | |
| Benzyl acetate | 9/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 15/50 |
| Butyl benzyl phthalate | 21/50 |
| D&C Yellow No. 11 | 16/50 |
| Emodin | 14/50 |
| *o*-Nitroanisole | 14/50 |
| *p*-Nitrobenzoic acid | 17/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | |
| Total (%) | 293/1,001 (29.3%) |
| Mean ± standard deviation | 29.3% ± 7.6% |
| Range | 16%-47% |

[a] Data as of January 17, 2001; includes data for lymphocytic, monocytic, and undifferentiated leukemia
[b] Data as of December 21, 1999; includes data for lymphocytic, monocytic, and undifferentiated leukemia

**TABLE B4c**
**Historical Incidence of Mammary Gland Fibroadenoma in Control Female F344/N Rats**

| Study | Incidence in Controls |
|---|---|
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | |
| Citral (feed) | 53/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 15/50 |
| Indium phosphide (inhalation) | 20/50 |
| 60-Hz Magnetic fields (whole body exposure) | 56/100 |
| Methacrylonitrile (gavage) | 21/50 |
| Naphthalene (inhalation) | 17/49 |
| *o*-Nitrotoluene (feed) | 23/60 |
| *p*-Nitrotoluene (feed) | 14/50 |
| Riddelliine (gavage) | 28/50 |
| Sodium nitrite (drinking water) | 21/50 |
| Vanadium pentoxide (inhalation) | 16/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | |
| Total (%) | 284/659 (43.1%) |
| Mean ± standard deviation | 41.1% ± 10.1% |
| Range | 28%-56% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | |
| Benzyl acetate | 12/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 25/50 |
| Butyl benzyl phthalate | 28/50 |
| D&C Yellow No. 11 | 21/50 |
| Emodin | 23/50 |
| *o*-Nitroanisole | 17/50 |
| *p*-Nitrobenzoic acid | 22/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | |
| Total (%) | 431/1,001 (43.1%) |
| Mean ± standard deviation | 43.1% ± 10.7% |
| Range | 24%-60% |

[a] Data as of January 17, 2001
[b] Data as of December 21, 1999

**TABLE B5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 7 | 12 | 10 | 7 |
| Natural deaths | 4 | 1 | 1 | 2 |
| Survivors | | | | |
| Terminal sacrifice | 39 | 37 | 39 | 41 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Intestine large, cecum | (50) | (49) | (50) | (50) |
| Edema | | 1 (2%) | | |
| Intestine small, ileum | (48) | (47) | (50) | (48) |
| Ulcer | | | 1 (2%) | |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | 1 (2%) | 2 (4%) |
| Basophilic focus | 44 (88%) | 41 (82%) | 49 (98%) | 46 (92%) |
| Clear cell focus | 12 (24%) | 11 (22%) | 18 (36%) | 10 (20%) |
| Cyst | | | | 1 (2%) |
| Eosinophilic focus | 1 (2%) | 2 (4%) | 7 (14%) | 9 (18%) |
| Fatty change | 1 (2%) | | | |
| Hematopoietic cell proliferation | 1 (2%) | 1 (2%) | | |
| Hepatodiaphragmatic nodule | 3 (6%) | 7 (14%) | 14 (28%) | 12 (24%) |
| Infiltration cellular, mixed cell | 41 (82%) | 33 (66%) | 43 (86%) | 49 (98%) |
| Mixed cell focus | 4 (8%) | 3 (6%) | 5 (10%) | 3 (6%) |
| Necrosis, focal | 1 (2%) | | 1 (2%) | 1 (2%) |
| Regeneration | | 1 (2%) | | |
| Bile duct, hyperplasia | 3 (6%) | 1 (2%) | | |
| Centrilobular, necrosis | 2 (4%) | | | |
| Hepatocyte, vacuolization cytoplasmic | 2 (4%) | 1 (2%) | | |
| Kupffer cell, pigmentation | 2 (4%) | 3 (6%) | | |
| Mesentery | (5) | (1) | (3) | |
| Fat, necrosis | 5 (100%) | 1 (100%) | 3 (100%) | |
| Pancreas | (50) | (50) | (50) | (50) |
| Atrophy | 3 (6%) | 1 (2%) | 8 (16%) | 4 (8%) |
| Acinus, hyperplasia, focal | | | 1 (2%) | 1 (2%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | | | 2 (4%) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Edema | 1 (2%) | 1 (2%) | | |
| Erosion | 1 (2%) | | | |
| Ulcer | 2 (4%) | | | |
| Epithelium, hyperplasia | 3 (6%) | 2 (4%) | 1 (2%) | |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Erosion | | 2 (4%) | | |
| Tooth | | (1) | | |
| Malformation | | 1 (100%) | | |

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

**TABLE B5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 13 (26%) | 10 (20%) | 11 (22%) | 8 (16%) |
| Inflammation, chronic | | | 3 (6%) | |
| Endocardium, fibrosis | 1 (2%) | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Accessory adrenal cortical nodule | 10 (20%) | 6 (12%) | 9 (18%) | 5 (10%) |
| Degeneration, fatty | 11 (22%) | 19 (38%) | 9 (18%) | 10 (20%) |
| Hyperplasia, focal | 5 (10%) | 8 (16%) | 3 (6%) | 3 (6%) |
| Hypertrophy | | | 2 (4%) | |
| Hypertrophy, focal | 4 (8%) | 14 (28%) | 7 (14%) | 2 (4%) |
| Necrosis | 1 (2%) | 1 (2%) | 1 (2%) | |
| Adrenal medulla | (49) | (50) | (50) | (50) |
| Hyperplasia | 3 (6%) | 2 (4%) | | |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Pars distalis, angiectasis | 4 (8%) | 5 (10%) | 7 (14%) | 7 (14%) |
| Pars distalis, cyst | 22 (44%) | 13 (26%) | 18 (36%) | 6 (12%) |
| Pars distalis, hyperplasia, focal | 10 (20%) | 12 (24%) | 8 (16%) | 7 (14%) |
| Pars intermedia, angiectasis | | | 2 (4%) | 2 (4%) |
| Pars intermedia, cyst | | 1 (2%) | 1 (2%) | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Ultimobranchial cyst | | | 1 (2%) | 2 (4%) |
| C-cell, hyperplasia | 16 (32%) | 14 (28%) | 13 (26%) | 8 (16%) |
| Follicle, cyst | | 1 (2%) | 1 (2%) | |
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Clitoral gland | (50) | (50) | (50) | (49) |
| Cyst | 2 (4%) | | | 1 (2%) |
| Hyperplasia | 3 (6%) | 5 (10%) | 4 (8%) | 6 (12%) |
| Inflammation, chronic | 2 (4%) | 3 (6%) | 2 (4%) | 2 (4%) |
| Ovary | (50) | (50) | (50) | (50) |
| Cyst | 9 (18%) | 11 (22%) | 3 (6%) | 6 (12%) |
| Uterus | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Prolapse | | | | 2 (4%) |
| Cervix, hyperplasia | 1 (2%) | | | |
| Endometrium, hyperplasia, cystic | 5 (10%) | 10 (20%) | 13 (26%) | 19 (38%) |
| Endometrium, hyperplasia, focal | | 1 (2%) | | |

**TABLE B5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hyperplasia | 4 (8%) | 3 (6%) | 6 (12%) | 7 (14%) |
| Infiltration cellular, histiocyte | | 1 (2%) | 1 (2%) | 5 (10%) |
| Lymph node | (4) | (8) | (3) | (11) |
| Hemorrhage | 1 (25%) | | | |
| Hyperplasia, lymphoid | | | | 1 (9%) |
| Pigmentation | 1 (25%) | | | |
| Iliac, pigmentation | | 1 (13%) | | |
| Mediastinal, hemorrhage | | 1 (13%) | | |
| Mediastinal, hyperplasia, lymphoid | | | | 1 (9%) |
| Mediastinal, pigmentation | | 1 (13%) | | |
| Pancreatic, ectasia | 1 (25%) | | | |
| Pancreatic, hemorrhage | | | 1 (33%) | 3 (27%) |
| Pancreatic, hyperplasia, histiocytic | 1 (25%) | 2 (25%) | 1 (33%) | 4 (36%) |
| Pancreatic, pigmentation | | | 1 (33%) | 4 (36%) |
| Renal, hemorrhage | | | | 1 (9%) |
| Renal, hyperplasia, lymphoid | | | | 1 (9%) |
| Renal, pigmentation | | 2 (25%) | | 2 (18%) |
| Lymph node, mandibular | (50) | (50) | (48) | (50) |
| Ectasia | 4 (8%) | 3 (6%) | 2 (4%) | 4 (8%) |
| Hemorrhage | 3 (6%) | 1 (2%) | 3 (6%) | 1 (2%) |
| Hyperplasia, lymphoid | 2 (4%) | 4 (8%) | 1 (2%) | 7 (14%) |
| Pigmentation | 27 (54%) | 22 (44%) | 24 (50%) | 25 (50%) |
| Lymph node, mesenteric | (49) | (50) | (50) | (50) |
| Hemorrhage | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Hyperplasia, lymphoid | | | | 1 (2%) |
| Pigmentation | 2 (4%) | 3 (6%) | 1 (2%) | |
| Spleen | (50) | (50) | (50) | (50) |
| Fibrosis | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Hematopoietic cell proliferation | 26 (52%) | 26 (52%) | 45 (90%) | 43 (86%) |
| Hemorrhage | | | | 1 (2%) |
| Infiltration cellular, mixed cell | | 1 (2%) | | |
| Pigmentation | 24 (48%) | 32 (64%) | 45 (90%) | 48 (96%) |
| Thymus | (48) | (48) | (45) | (50) |
| Cyst | | 1 (2%) | | 1 (2%) |
| Hyperplasia, lymphoid | | | | 1 (2%) |
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Hyperplasia | 42 (84%) | 42 (84%) | 45 (90%) | 29 (58%) |
| Skin | (50) | (50) | (50) | (49) |
| Cyst epithelial inclusion | 1 (2%) | 1 (2%) | | |
| Ulcer | 1 (2%) | 2 (4%) | | 2 (4%) |
| Epidermis, hyperplasia | 1 (2%) | 3 (6%) | | 1 (2%) |
| **Musculoskeletal System** | | | | |
| Bone | (49) | (50) | (50) | (50) |
| Cranium, osteopetrosis | 12 (24%) | 12 (24%) | 11 (22%) | 11 (22%) |
| Femur, osteopetrosis | 19 (39%) | 14 (28%) | 10 (20%) | 6 (12%) |

**TABLE B5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Compression | 4 (8%) | 6 (12%) | 3 (6%) | 3 (6%) |
| Hydrocephalus | 1 (2%) | 4 (8%) | 1 (2%) | 1 (2%) |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Hemorrhage | 1 (2%) | | 2 (4%) | |
| Infiltration cellular, histiocyte | 44 (88%) | 35 (70%) | 39 (78%) | 31 (62%) |
| Metaplasia, osseous | 1 (2%) | 1 (2%) | | |
| Alveolar epithelium, hyperplasia | 4 (8%) | 5 (10%) | 4 (8%) | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |
| Foreign body | 3 (6%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Inflammation, chronic | 5 (10%) | 4 (8%) | 2 (4%) | |
| Respiratory epithelium, hyperplasia | 1 (2%) | | 3 (6%) | 1 (2%) |
| Respiratory epithelium, metaplasia, squamous | | 2 (4%) | 1 (2%) | |
| **Special Senses System** | | | | |
| Eye | (2) | | (3) | (1) |
| Cataract | 1 (50%) | | 3 (100%) | 1 (100%) |
| Inflammation, chronic | 1 (50%) | | | |
| Retina, degeneration | 1 (50%) | | 3 (100%) | 1 (100%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Cyst | 1 (2%) | | | |
| Glomerulosclerosis | | 1 (2%) | | |
| Hydronephrosis | 1 (2%) | | | |
| Infarct | 1 (2%) | | | 2 (4%) |
| Inflammation, chronic | 2 (4%) | | | 2 (4%) |
| Mineralization | 15 (30%) | 21 (42%) | 32 (64%) | 40 (80%) |
| Nephropathy | 11 (22%) | 12 (24%) | 7 (14%) | 11 (22%) |
| Renal tubule, dilatation | 1 (2%) | 1 (2%) | | 1 (2%) |
| Renal tubule, hyaline droplet | 8 (16%) | 41 (82%) | 49 (98%) | 46 (92%) |
| Renal tubule, hyperplasia | 1 (2%) | | | |
| Renal tubule, hyperplasia, oncocytic | | 2 (4%) | 4 (8%) | 6 (12%) |
| Renal tubule, pigmentation | 9 (18%) | 43 (86%) | 49 (98%) | 50 (100%) |
| Transitional epithelium, hyperplasia | 3 (6%) | | | |
| Urinary bladder | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Transitional epithelium, hyperplasia | | | | 1 (2%) |

# APPENDIX C
# SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF *p*-NITROTOLUENE

**TABLE C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 2 | 3 | 6 |
| Natural deaths | 2 | 2 | 2 | 2 |
| Survivors | | | | |
| Terminal sacrifice | 46 | 46 | 45 | 42 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Intestine large, cecum | (48) | (48) | (48) | (49) |
| Carcinoma | 1 (2%) | | | |
| Intestine small, duodenum | (48) | (49) | (49) | (49) |
| Polyp adenomatous | | 2 (4%) | | |
| Intestine small, jejunum | (48) | (49) | (48) | (49) |
| Carcinoma | | 1 (2%) | | |
| Polyp adenomatous | | | | 1 (2%) |
| Intestine small, ileum | (48) | (49) | (48) | (49) |
| Liver | (50) | (50) | (50) | (50) |
| Cholangiocarcinoma | | 1 (2%) | | |
| Hemangiosarcoma | 1 (2%) | | 1 (2%) | |
| Hepatoblastoma | | | | 1 (2%) |
| Hepatocellular carcinoma | 8 (16%) | 11 (22%) | 10 (20%) | 12 (24%) |
| Hepatocellular carcinoma, multiple | | 1 (2%) | 1 (2%) | |
| Hepatocellular adenoma | 13 (26%) | 9 (18%) | 12 (24%) | 11 (22%) |
| Hepatocellular adenoma, multiple | 1 (2%) | 4 (8%) | 3 (6%) | 4 (8%) |
| Hepatocholangiocarcinoma | 2 (4%) | | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | 1 (2%) | 1 (2%) |
| Ito cell tumor malignant | | | 1 (2%) | |
| Mesentery | (6) | (7) | (8) | (5) |
| Cholangiocarcinoma, metastatic, liver | | 1 (14%) | | |
| Hemangiosarcoma | | | 1 (13%) | 1 (20%) |
| Hepatocholangiocarcinoma, metastatic, liver | 1 (17%) | | 1 (13%) | |
| Histiocytic sarcoma | 1 (17%) | | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Cholangiocarcinoma, metastatic, liver | | 1 (2%) | | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | 2 (4%) | 2 (4%) | 3 (6%) |
| Tongue | | | (1) | |
| Squamous cell carcinoma | | | 1 (100%) | |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |

**TABLE C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Endocrine System** | | | | |
| Adrenal cortex | (49) | (50) | (49) | (50) |
| Adenoma | 2 (4%) | 1 (2%) | | 1 (2%) |
| Capsule, adenoma | 2 (4%) | 3 (6%) | 3 (6%) | |
| Subcapsular, adenoma | | | | 1 (2%) |
| Adrenal medulla | (49) | (50) | (49) | (49) |
| Pheochromocytoma benign | | | 1 (2%) | |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Adenoma | | | | 1 (2%) |
| Pituitary gland | (46) | (49) | (49) | (45) |
| Pars intermedia, adenoma | | 1 (2%) | | |
| Thyroid gland | (50) | (50) | (49) | (49) |
| Follicular cell, adenoma | | | | 2 (4%) |
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Prostate | (50) | (50) | (49) | (50) |
| Testes | (50) | (50) | (50) | (50) |
| Interstitial cell, adenoma | | 1 (2%) | | 1 (2%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hemangioma | | 1 (2%) | | |
| Lymph node | (5) | (5) | (3) | (5) |
| Renal, hepatocholangiocarcinoma, metastatic, liver | 1 (20%) | | | |
| Lymph node, mandibular | (48) | (50) | (45) | (48) |
| Lymph node, mesenteric | (50) | (49) | (49) | (49) |
| Hepatocholangiocarcinoma, metastatic, liver | | | 1 (2%) | |
| Histiocytic sarcoma | | | | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Hemangioma | | 1 (2%) | | |
| Hemangiosarcoma | | 1 (2%) | 1 (2%) | 1 (2%) |
| Thymus | (47) | (40) | (44) | (45) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| **Integumentary System** | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | | | |
| Subcutaneous tissue, fibrosarcoma | | 1 (2%) | | |
| **Musculoskeletal System** | | | | |
| Skeletal muscle | (1) | (1) | (1) | |
| Cholangiocarcinoma, metastatic, liver | | 1 (100%) | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | 1 (100%) | |

**TABLE C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Nervous System** | | | | |
| None | | | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 5 (10%) | 8 (16%) | 6 (12%) | 11 (22%) |
| Alveolar/bronchiolar adenoma, multiple | 1 (2%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | 5 (10%) | 4 (8%) | 4 (8%) |
| Alveolar/bronchiolar carcinoma, multiple | 1 (2%) | 1 (2%) | | 2 (4%) |
| Cholangiocarcinoma, metastatic, liver | | 1 (2%) | | |
| Hepatocellular carcinoma, metastatic, liver | 1 (2%) | 3 (6%) | 1 (2%) | |
| Hepatocholangiocarcinoma, metastatic, liver | | | 1 (2%) | |
| Histiocytic sarcoma | | | 1 (2%) | |
| Mediastinum, fibrosarcoma, metastatic, skin | | 1 (2%) | | |
| Mediastinum, hepatocholangiocarcinoma, metastatic, liver | | | 1 (2%) | |
| Mediastinum, histiocytic sarcoma | 1 (2%) | | | |
| **Special Senses System** | | | | |
| Harderian gland | (3) | (4) | (6) | (2) |
| Adenoma | 3 (100%) | 3 (75%) | 6 (100%) | 1 (50%) |
| Carcinoma | | 1 (25%) | | 1 (50%) |
| **Urinary System** | | | | |
| Kidney | (50) | (49) | (50) | (50) |
| Renal tubule, adenoma | | 1 (2%) | | |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | 1 (2%) | | 1 (2%) | 2 (4%) |
| Lymphoma malignant | 3 (6%) | 3 (6%) | 1 (2%) | 4 (8%) |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | 31 | 38 | 41 | 44 |
| Total primary neoplasms | 47 | 64 | 58 | 67 |
| Total animals with benign neoplasms | 25 | 28 | 30 | 33 |
| Total benign neoplasms | 29 | 38 | 35 | 39 |
| Total animals with malignant neoplasms | 14 | 24 | 20 | 21 |
| Total malignant neoplasms | 18 | 26 | 23 | 28 |
| Total animals with metastatic neoplasms | 2 | 5 | 2 | |
| Total metastatic neoplasms | 3 | 8 | 6 | |

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 4 5 3 | 6 6 5 | 7 1 7 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 9 | 0 4 1 | 0 1 3 | 0 3 8 | 0 0 1 | 0 0 4 | 0 0 5 | 0 1 0 | 0 1 1 | 0 1 2 | 0 1 4 | 0 1 7 | 0 2 2 | 0 2 3 | 0 2 8 | 0 3 1 | 0 4 2 | 0 4 6 | 0 5 0 | 0 0 7 | 0 0 8 | 0 2 0 | 0 2 1 | 0 2 4 | 0 2 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine small, duodenum | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | X | | | X | | X | | | | | | | | | | X | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | X | | | | | | | | | | | | | X | X | X | X | X |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Mesentery | | + | | | + | | | + | | | | | | | | | | | + | | | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | + | | | + | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | X | X | | | | | | | | | | | | | | | | | | | |
| Capsule, adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 6 | 0 3 7 | 0 4 3 | 0 4 7 | 0 4 8 | 0 0 2 | 0 0 3 | 0 0 6 | 0 1 6 | 0 1 8 | 0 2 6 | 0 2 7 | 0 3 0 | 0 3 2 | 0 3 3 | 0 3 4 | 0 3 5 | 0 3 9 | 0 4 0 | 0 4 9 | 0 0 9 | 0 1 5 | 0 1 9 | 0 4 4 | 0 4 5 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Hepatocellular carcinoma | | X | | | | | | | | | | | | | | | | X | | | | | | X | X | 8 |
| Hepatocellular adenoma | | | | | X | | | X | | | | | X | | X | | X | | | X | | | | | X | 13 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Hepatocholangiocarcinoma | | | | | X | | | | | | | | | | | | | | X | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | + | | | | | | | | | | | | | | + | | | | | | | 6 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Tooth | | | | | | | | | + | | + | | | | + | | | | | | | + | | | | 6 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Capsule, adenoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | M | + | + | + | 46 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 4 5 3 | 6 6 5 | 7 1 7 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 9 | 0 4 1 | 0 1 3 | 0 3 8 | 0 0 1 | 0 0 4 | 0 0 5 | 0 1 0 | 0 1 1 | 0 1 2 | 0 1 4 | 0 1 7 | 0 2 2 | 0 2 3 | 0 2 8 | 0 3 1 | 0 4 2 | 0 4 6 | 0 5 0 | 0 7 | 0 8 | 0 2 0 | 0 2 1 | 0 2 4 | 0 2 5 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | | | | + | | + | | + | | | | | | | |
| Renal, hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| **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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | + | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | + | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | + | | | | | | | | | | | | | | | | + | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | X | | | | | | | | | | | | | | | | X | | | | | | | |
| Alveolar/bronchiolar adenoma, multiple | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 6 | 0 3 7 | 0 4 3 | 0 4 7 | 0 4 8 | 0 0 2 | 0 0 3 | 0 0 6 | 0 1 6 | 0 1 8 | 0 2 6 | 0 2 7 | 0 3 0 | 0 3 2 | 0 3 3 | 0 3 4 | 0 3 5 | 0 3 9 | 0 4 0 | 0 4 9 | 0 0 9 | 0 1 5 | 0 1 9 | 0 4 4 | 0 4 5 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | + | | | | | | | | | | | | | | | | | + | | | | 5 |
| Renal, hepatocholangiocarcinoma, metastatic, liver | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 47 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | + | M | M | M | M | M | M | M | M | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | X | | X | | X | | | | | | | | | | | | | | | | | | 5 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinum, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 4 5 3 | 6 6 5 | 7 1 7 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 9 | 0 4 1 | 0 1 3 | 0 3 8 | 0 0 1 | 0 0 4 | 0 0 5 | 0 1 0 | 0 1 1 | 0 1 2 | 0 1 4 | 0 1 7 | 0 2 2 | 0 2 3 | 0 2 8 | 0 3 1 | 0 4 2 | 0 4 6 | 0 5 0 | 0 0 7 | 0 0 8 | 0 2 0 | 0 2 1 | 0 2 4 | 0 2 5 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | X | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 2 8 0 | 6 8 9 | 7 1 1 | 7 1 5 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 0 6 6 | 0 0 5 4 | 0 0 7 8 | 0 0 6 7 | 0 0 5 8 | 0 0 5 9 | 0 0 6 2 | 0 0 8 0 | 0 0 8 4 | 0 0 8 5 | 0 0 8 8 | 0 0 9 4 | 0 0 9 5 | 0 0 9 6 | 0 0 5 1 | 0 0 6 8 | 0 0 7 0 | 0 0 7 6 | 0 0 7 7 | 0 0 9 1 | 0 0 9 2 | 0 0 9 7 | 0 0 9 9 | 0 0 5 2 | 0 0 5 3 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | M | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | | | | | X | X | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine small, ileum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cholangiocarcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | X | | X | | | | | X | X | | | X | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | X | X | | | | | X | | | | X | | | | | | | | X | | X |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | X | | X | | | | | | | |
| Mesentery | + | | | + | | | | | | | + | | | | | | | + | | + | | | | | |
| Cholangiocarcinoma, metastatic, liver | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cholangiocarcinoma, metastatic, liver | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Stomach, glandular | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | + | | | + | + | | | | | | | + | | | | + | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | M |
| Pituitary gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars intermedia, adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 5 5 | 0 5 6 | 0 5 7 | 0 6 1 | 0 6 3 | 0 6 4 | 0 6 5 | 0 6 9 | 0 7 1 | 0 7 2 | 0 7 3 | 0 7 4 | 0 7 5 | 0 7 9 | 0 8 6 | 0 8 7 | 0 8 9 | 0 9 0 | 0 9 3 | 0 9 8 | 0 6 0 | 0 8 1 | 0 8 2 | 0 8 3 | 1 0 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | X | | | X | | | | | X | | | | | | | | | X | | | | X | X | | 11 |
| Hepatocellular carcinoma, multiple | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular adenoma | | | | | | X | | | | | | X | | X | | | | | | | | | | | | 9 |
| Hepatocellular adenoma, multiple | | | | X | | | | X | | | | | | | | | | | | | | | | | | 4 |
| Mesentery | | | | | | | | | | | | | | | | | | | | + | | | + | | | 7 |
| Cholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Tooth | | + | + | | | + | | | + | + | | | | + | + | | | | | | | | | + | | 13 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Capsule, adenoma | X | | | | | | | | | | | | | | | | | X | | | | | | | | 3 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | M | 45 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | + | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 28 | 68 | 71 | 71 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 80 | 89 | 01 | 15 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 30 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 01 | 01 |
| **Carcass ID Number** | 06 | 05 | 07 | 06 | 05 | 05 | 06 | 08 | 08 | 08 | 08 | 09 | 09 | 09 | 05 | 06 | 07 | 07 | 09 | 09 | 09 | 09 | 05 | 05 | 05 |
| | 66 | 64 | 68 | 67 | 68 | 69 | 62 | 00 | 04 | 45 | 88 | 44 | 55 | 96 | 11 | 68 | 00 | 66 | 71 | 12 | 27 | 99 | 22 | 23 | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Lymph node | | | | | | | | | | | | | | | | | | + | | + | | | + | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | 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 | M |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, fibrosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | + | | | | | | | | | | | | | | | | | | | | | |
| Cholangiocarcinoma, metastatic, liver | | | | X | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | X | | | | | | | X | X | X | | | | | | |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | X | | | | | | | | | | | | | X | | | | | | | X | | | |
| Alveolar/bronchiolar carcinoma, multiple | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Cholangiocarcinoma, metastatic, liver | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Mediastinum, fibrosarcoma, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | + | |
| Harderian gland | | | | | | | | | | | | | | | | | | + | | | | | | + | |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | X | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 5 5 | 0 5 6 | 0 5 7 | 0 6 1 | 0 6 3 | 0 6 4 | 0 6 5 | 0 6 9 | 0 7 1 | 0 7 2 | 0 7 3 | 0 7 4 | 0 7 5 | 0 7 9 | 0 8 6 | 0 8 7 | 0 8 9 | 0 9 0 | 0 9 3 | 0 9 8 | 0 6 0 | 0 8 1 | 0 8 2 | 0 8 3 | 1 0 0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | + | | | | | | | | | | | | | | | | | | | | | + | | | 5 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | M | + | + | + | + | + | + | + | M | + | I | + | + | + | + | + | + | + | + | + | + | + | M | + | 40 |
| **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 | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Cholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | X | | | | | | | | | | | | | | | X | | X | X | | | | 8 |
| Alveolar/bronchiolar adenoma, multiple | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | X | | | | | | | | | | | | | | | | | | | | X | | | | 5 |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Cholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | X | | | | | | | | | | | | | | | | | | | | | | X | | 3 |
| Mediastinum, fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | + | | | | | | | | | | | | | | | | | | | | | + | 4 |
| Adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | X | 3 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Renal tubule, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | X | | X | 3 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 5 9 7 | 5 9 7 | 6 2 5 | 6 8 9 | 6 9 3 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 0 4 | 1 5 0 | 1 4 6 | 1 4 2 | 1 2 7 | 1 1 3 | 1 2 0 | 1 2 1 | 1 2 1 4 | 1 2 2 5 | 1 2 4 4 | 1 4 4 7 | 1 0 1 | 1 0 9 | 1 1 0 | 1 1 2 | 1 1 4 | 1 1 5 | 1 1 9 | 1 2 3 | 1 2 8 | 1 2 9 | 1 3 3 | 1 3 5 | 1 3 6 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | X | | | | | | | | X | X | | | | | X | | X | | X | | | | |
| Hepatocellular carcinoma, multiple | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | X | | | | | | | | X | X | X | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | X | | | | X | | | | | | | | |
| Hepatocholangiocarcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Ito cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | + | + | | | + | | | | | + | | | | | | | | | + | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | + | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Tooth | | | | | | | | + | | | | | + | | | | | | + | | + | + | | + | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, adenoma | | | | | | | | X | | | | | | X | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | M | M | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 8 | 1 4 1 | 1 4 8 | 1 4 9 | 1 0 3 | 1 0 5 | 1 0 6 | 1 0 7 | 1 1 1 | 1 1 6 | 1 3 2 | 1 4 0 | 1 4 5 | 1 0 2 | 1 0 8 | 1 1 7 | 1 1 8 | 1 2 2 | 1 2 6 | 1 3 0 | 1 3 1 | 1 3 4 | 1 3 7 | 1 3 9 | 1 4 3 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | 48 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | | X | | | X | | | | | | | | | | X | X | | | | | | | 10 |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular adenoma | | | X | | | X | X | | X | | | X | | | X | X | | | | | | | | X | | 12 |
| Hepatocellular adenoma, multiple | | | | | | | | | | | X | | | | | | | | | | | | | | | 3 |
| Hepatocholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ito cell tumor malignant | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | + | | | | + | | | | | | + | | | | | | | | | | | | | | | 8 |
| Hemangiosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | X | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | + | + | | 8 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | + | | | | | | | | | | | | | | | | | 1 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 3 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | M | 44 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 8 | 1 4 1 | 1 4 8 | 1 4 9 | 1 0 3 | 1 0 5 | 1 0 6 | 1 0 7 | 1 1 1 | 1 1 6 | 1 3 2 | 1 4 0 | 1 4 5 | 1 0 2 | 1 0 8 | 1 1 7 | 1 1 8 | 1 2 2 | 1 2 6 | 1 3 0 | 1 3 1 | 1 3 4 | 1 3 7 | 1 3 9 | 1 4 3 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulating gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | + | | | + | | | | | | | | | + | | | 3 |
| Lymph node, mandibular | M | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + | + | M | 45 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | 49 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | 44 |
| **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 | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | X | | X | | X | | | 6 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | X | X | | | | | X | | | | | | | | | | | | | | | | | | X | 4 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinum, hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | + | | | | | | | | | + | + | + | | | | | | + | | | | | | 6 |
| Adenoma | | | X | | | | | | | | | X | X | X | | | | | | X | | | | | | 6 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| **Number of Days on Study** | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 13038 | 14041 | 14048 | 14049 | 10033 | 10055 | 10066 | 10077 | 11011 | 11016 | 13032 | 14040 | 14045 | 10028 | 10085 | 11017 | 11822 | 12226 | 13030 | 13314 | 13347 | 13379 | 13393 | 14043 | | Total Tissues/ Tumors |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 5 0 5 | 5 8 5 | 5 9 7 | 6 2 5 | 6 8 1 | 6 8 9 | 7 1 4 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 7 6 | 1 6 0 | 1 9 8 | 1 6 4 | 1 9 6 | 1 9 1 | 1 7 9 | 1 5 9 | 1 5 3 | 1 5 8 | 1 7 2 | 1 7 3 | 1 8 4 | 1 8 7 | 1 9 0 | 1 9 2 | 1 6 1 | 1 6 5 | 1 7 8 | 1 8 3 | 1 9 4 | 1 9 5 | 1 9 7 | 2 0 0 | 1 5 2 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | A | + | + | A | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatoblastoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | X | | X | | | X | | | | | | X | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | X | | | X | | | | | X | | X | | X | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | X | | | | | | | | | | | | | X | |
| Histiocytic sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | + | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | + | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | X | X | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | + | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Subcapsular, adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | I | M | + | + | I | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 5 7 | 1 6 2 | 1 6 7 | 1 6 8 | 1 6 9 | 1 7 1 | 1 7 5 | 1 7 7 | 1 8 1 | 1 8 5 | 1 8 6 | 1 8 8 | 1 9 3 | 1 5 1 | 1 5 4 | 1 5 5 | 1 5 6 | 1 6 3 | 1 6 6 | 1 7 0 | 1 7 4 | 1 8 0 | 1 8 2 | 1 8 9 | 1 9 9 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatoblastoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | X | | X | | | X | X | | X | X | X | X | | | | | | | | | | | 12 |
| Hepatocellular adenoma | | | | | | | X | | | X | | X | X | | | X | X | | | | | | | | | 11 |
| Hepatocellular adenoma, multiple | X | | | | X | | | | | | | | | | | | | | | | | | | | | 4 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | + | | | | | + | | | | | | | | | | | | | | + | | | + | | | 5 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | X | | | | | | 3 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tooth | | + | | + | | | | | | + | | | + | + | | | + | | | | | | | | + | 8 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcapsular, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | 45 |
| Thyroid gland | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Follicular cell, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 5 0 5 | 5 8 5 | 5 9 7 | 6 2 5 | 6 8 1 | 6 8 9 | 7 1 4 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 7 7 6 | 1 6 0 | 1 9 8 | 1 6 4 | 1 9 6 | 1 9 1 | 1 7 9 | 1 5 9 | 1 5 3 | 1 5 8 | 1 7 2 | 1 7 3 | 1 8 4 | 1 8 7 | 1 9 0 | 1 9 2 | 1 6 1 | 1 6 5 | 1 7 8 | 1 8 3 | 1 9 4 | 1 9 5 | 1 9 7 | 2 0 0 | 1 5 2 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | | | | | + | | + | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Thymus | + | + | M | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + |
| Histiocytic sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | X | | | | X | | | | | | | | | | X | X | X | | | | | | | | |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Alveolar/bronchiolar carcinoma | | X | X | | | | | | X | | | | | | | | | | | | | X | | | |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | X | | | | | | X | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | + | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | X | | | | | X | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | X | | | | | | | | X | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 5 7 | 1 6 2 | 1 6 7 | 1 6 8 | 1 6 9 | 1 7 1 | 1 7 5 | 1 7 7 | 1 8 1 | 1 8 5 | 1 8 6 | 1 8 8 | 1 9 3 | 1 1 1 | 1 5 4 | 1 5 5 | 1 5 6 | 1 6 3 | 1 6 6 | 1 7 0 | 1 7 4 | 1 8 0 | 1 8 2 | 1 8 9 | 1 9 9 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | + | | | | | | | | | | | | + | | | | | | | | 5 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | M | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | 45 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | + | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | X | X | | | | X | | | | X | | | | | | | | | | | | X | X | 11 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | X | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | + | | | 2 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Lymphoma malignant | | | | | | X | | | | | | | | | | | X | | | | | | | | | 4 |

**TABLE C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Adrenal Cortex: Adenoma** | | | | |
| Overall rate[a] | 3/49 (6%) | 4/50 (8%) | 3/49 (6%) | 2/50 (4%) |
| Adjusted rate[b] | 6.3% | 8.2% | 6.3% | 4.2% |
| Terminal rate[c] | 3/45 (7%) | 4/46 (9%) | 3/45 (7%) | 2/42 (5%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test[d] | P=0.352N | P=0.510 | P=0.659 | P=0.503N |
| **Harderian Gland: Adenoma** | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 6/50 (12%) | 1/50 (2%) |
| Adjusted rate | 6.1% | 6.2% | 12.4% | 2.1% |
| Terminal rate | 3/46 (7%) | 3/46 (7%) | 6/45 (13%) | 1/42 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.314N | P=0.660 | P=0.238 | P=0.315N |
| **Harderian Gland: Adenoma or Carcinoma** | | | | |
| Overall rate | 3/50 (6%) | 4/50 (8%) | 6/50 (12%) | 2/50 (4%) |
| Adjusted rate | 6.1% | 8.2% | 12.4% | 4.2% |
| Terminal rate | 3/46 (7%) | 4/46 (9%) | 6/45 (13%) | 1/42 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 681 |
| Poly-3 test | P=0.428N | P=0.498 | P=0.238 | P=0.511N |
| **Liver: Hepatocellular Adenoma** | | | | |
| Overall rate | 14/50 (28%) | 13/50 (26%) | 15/50 (30%) | 15/50 (30%) |
| Adjusted rate | 28.6% | 26.7% | 31.0% | 31.5% |
| Terminal rate | 14/46 (30%) | 13/46 (28%) | 15/45 (33%) | 15/42 (36%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.370 | P=0.504N | P=0.487 | P=0.465 |
| **Liver: Hepatocellular Carcinoma** | | | | |
| Overall rate | 8/50 (16%) | 12/50 (24%) | 11/50 (22%) | 12/50 (24%) |
| Adjusted rate | 16.1% | 24.6% | 22.3% | 24.7% |
| Terminal rate | 6/46 (13%) | 12/46 (26%) | 9/45 (20%) | 9/42 (21%) |
| First incidence (days) | 453 | 729 (T) | 597 | 585 |
| Poly-3 test | P=0.233 | P=0.213 | P=0.298 | P=0.209 |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | | |
| Overall rate | 20/50 (40%) | 24/50 (48%) | 25/50 (50%) | 24/50 (48%) |
| Adjusted rate | 40.2% | 49.2% | 50.8% | 49.5% |
| Terminal rate | 18/46 (39%) | 24/46 (52%) | 23/45 (51%) | 21/42 (50%) |
| First incidence (days) | 453 | 729 (T) | 597 | 585 |
| Poly-3 test | P=0.239 | P=0.245 | P=0.198 | P=0.237 |
| **Liver: Hepatocellular Carcinoma or Hepatoblastoma** | | | | |
| Overall rate | 8/50 (16%) | 12/50 (24%) | 11/50 (22%) | 13/50 (26%) |
| Adjusted rate | 16.1% | 24.6% | 22.3% | 26.8% |
| Terminal rate | 6/46 (13%) | 12/46 (26%) | 9/45 (20%) | 9/42 (21%) |
| First incidence (days) | 453 | 729 (T) | 597 | 585 |
| Poly-3 test | P=0.163 | P=0.213 | P=0.298 | P=0.148 |
| **Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma** | | | | |
| Overall rate | 20/50 (40%) | 24/50 (48%) | 25/50 (50%) | 25/50 (50%) |
| Adjusted rate | 40.2% | 49.2% | 50.8% | 51.5% |
| Terminal rate | 18/46 (39%) | 24/46 (52%) | 23/45 (51%) | 21/42 (50%) |
| First incidence (days) | 453 | 729 (T) | 597 | 585 |
| Poly-3 test | P=0.178 | P=0.245 | P=0.198 | P=0.179 |

**TABLE C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Lung: Alveolar/bronchiolar Adenoma** | | | | |
| Overall rate | 6/50 (12%) | 9/50 (18%) | 8/50 (16%) | 13/50 (26%) |
| Adjusted rate | 12.2% | 18.5% | 16.5% | 26.8% |
| Terminal rate | 4/46 (9%) | 9/46 (20%) | 7/45 (16%) | 11/42 (26%) |
| First incidence (days) | 665 | 729 (T) | 693 | 505 |
| Poly-3 test | P=0.049 | P=0.282 | P=0.377 | P=0.057 |
| **Lung: Alveolar/bronchiolar Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 6/50 (12%) | 4/50 (8%) | 6/50 (12%) |
| Adjusted rate | 4.1% | 12.2% | 8.3% | 12.3% |
| Terminal rate | 2/46 (4%) | 4/46 (9%) | 4/45 (9%) | 3/42 (7%) |
| First incidence (days) | 729 (T) | 689 | 729 (T) | 585 |
| Poly-3 test | P=0.176 | P=0.134 | P=0.333 | P=0.132 |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | | |
| Overall rate | 8/50 (16%) | 14/50 (28%) | 12/50 (24%) | 19/50 (38%) |
| Adjusted rate | 16.3% | 28.6% | 24.7% | 38.4% |
| Terminal rate | 6/46 (13%) | 12/46 (26%) | 11/45 (24%) | 14/42 (33%) |
| First incidence (days) | 665 | 689 | 693 | 505 |
| Poly-3 test | P=0.014 | P=0.111 | P=0.217 | P=0.011 |
| **Stomach (Forestomach): Squamous Cell Papilloma** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 2.0% | 4.1% | 4.1% | 6.2% |
| Terminal rate | 1/46 (2%) | 2/46 (4%) | 2/45 (4%) | 1/42 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 625 |
| Poly-3 test | P=0.228 | P=0.499 | P=0.497 | P=0.300 |
| **All Organs: Hemangiosarcoma** | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted rate | 2.0% | 2.1% | 6.2% | 4.2% |
| Terminal rate | 1/46 (2%) | 1/46 (2%) | 2/45 (4%) | 2/42 (5%) |
| First incidence (days) | 729 (T) | 729 (T) | 689 | 729 (T) |
| Poly-3 test | P=0.312 | P=0.760 | P=0.303 | P=0.490 |
| **All Organs: Hemangioma or Hemangiosarcoma** | | | | |
| Overall rate | 1/50 (2%) | 3/50 (6%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted rate | 2.0% | 6.1% | 6.2% | 4.2% |
| Terminal rate | 1/46 (2%) | 2/46 (4%) | 2/45 (4%) | 2/42 (5%) |
| First incidence (days) | 729 (T) | 689 | 689 | 729 (T) |
| Poly-3 test | P=0.460 | P=0.306 | P=0.303 | P=0.490 |
| **All Organs: Malignant Lymphoma** | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 1/50 (2%) | 4/50 (8%) |
| Adjusted rate | 6.1% | 6.2% | 2.1% | 8.4% |
| Terminal rate | 3/46 (7%) | 3/46 (7%) | 1/45 (2%) | 3/42 (7%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 681 |
| Poly-3 test | P=0.428 | P=0.660 | P=0.309N | P=0.487 |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 25/50 (50%) | 28/50 (56%) | 30/50 (60%) | 33/50 (66%) |
| Adjusted rate | 50.8% | 57.2% | 61.8% | 67.4% |
| Terminal rate | 23/46 (50%) | 27/46 (59%) | 29/45 (64%) | 29/42 (69%) |
| First incidence (days) | 665 | 689 | 693 | 505 |
| Poly-3 test | P=0.054 | P=0.332 | P=0.186 | P=0.069 |

**TABLE C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 14/50 (28%) | 24/50 (48%) | 20/50 (40%) | 21/50 (42%) |
| Adjusted rate | 28.2% | 48.0% | 40.0% | 42.7% |
| Terminal rate | 12/46 (26%) | 20/46 (44%) | 15/45 (33%) | 15/42 (36%) |
| First incidence (days) | 453 | 280 | 597 | 585 |
| Poly-3 test | P=0.181 | P=0.032 | P=0.151 | P=0.096 |
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 31/50 (62%) | 38/50 (76%) | 41/50 (82%) | 44/50 (88%) |
| Adjusted rate | 62.0% | 76.0% | 82.0% | 88.0% |
| Terminal rate | 27/46 (59%) | 34/46 (74%) | 36/45 (80%) | 36/42 (86%) |
| First incidence (days) | 453 | 280 | 597 | 505 |
| Poly-3 test | P=0.002 | P=0.097 | P=0.021 | P=0.002 |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

**TABLE C4**
**Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male B6C3F$_1$ Mice**

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence in Controls Given NTP-2000 Diet**[a] | | | |
| Acrylonitrile (gavage) | 10/50 | 4/50 | 14/50 |
| Citral (feed) | 12/100 | 9/100 | 20/100 |
| *p,p′*-Dichlorodiphenyl sulfone (feed) | 6/50 | 7/50 | 13/50 |
| Indium phosphide (inhalation) | 13/50 | 6/50 | 18/50 |
| 60-Hz Magnetic fields (whole body exposure) | 26/100 | 8/100 | 30/100 |
| Methacrylonitrile (gavage) | 2/49 | 4/49 | 6/49 |
| *o*-Nitrotoluene (feed) | 9/60 | 5/60 | 14/60 |
| *p*-Nitrotoluene (feed) | 6/50 | 2/50 | 8/50 |
| Riddelliine (gavage) | 12/50 | 7/50 | 18/50 |
| Sodium nitrite (drinking water) | 10/50 | 4/50 | 13/50 |
| Vanadium pentoxide (inhalation) | 13/50 | 12/50 | 22/50 |
| **Overall Historical Incidence in Controls Given NTP-2000 Diet** | | | |
| Total (%) | 119/659 (18.1%) | 68/659 (10.3%) | 176/659 (26.7%) |
| Mean ± standard deviation | 17.9% ± 7.4% | 10.7% ± 5.3% | 27.1% ± 9.3% |
| Range | 4%-26% | 4%-24% | 12%-44% |
| **Historical Incidence in Feed Controls Given NIH-07 Diet at Southern Research Institute**[b] | | | |
| Benzyl acetate | 9/50 | 5/50 | 14/50 |
| 2,2-Bis(bromomethyl)-1,3-propanediol | 12/50 | 3/50 | 15/50 |
| *t*-Butylhydroquinone | 12/50 | 3/50 | 15/50 |
| Emodin | 9/50 | 10/50 | 18/50 |
| *o*-Nitroanisole | 5/50 | 1/50 | 6/50 |
| *p*-Nitrobenzoic acid | 6/50 | 1/50 | 7/50 |
| **Overall Historical Incidence in Feed Controls Given NIH-07 Diet** | | | |
| Total (%) | 172/952 (18.1%) | 72/952 (7.6%) | 236/952 (24.8%) |
| Mean ± standard deviation | 18.1% ± 6.7% | 7.6% ± 5.2% | 24.8% ± 7.0% |
| Range | 6%-30% | 2%-20% | 12%-36% |

[a] Data as of December 20, 2000
[b] Data as of December 23, 1999

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 2 | 3 | 6 |
| Natural deaths | 2 | 2 | 2 | 2 |
| Survivors | | | | |
| Terminal sacrifice | 46 | 46 | 45 | 42 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Gallbladder | (49) | (48) | (48) | (47) |
| Inflammation, chronic | 1 (2%) | | | |
| Epithelium, hyperplasia | 1 (2%) | | | |
| Intestine small, duodenum | (48) | (49) | (49) | (49) |
| Ectasia | | | | 1 (2%) |
| Inflammation, chronic, focal | | | | 1 (2%) |
| Necrosis, focal | | | | 1 (2%) |
| Epithelium, hyperplasia, focal | | | | 1 (2%) |
| Intestine small, jejunum | (48) | (49) | (48) | (49) |
| Epithelium, hyperplasia, focal | 1 (2%) | | | |
| Peyer's patch, hyperplasia, lymphoid | | | | 2 (4%) |
| Peyer's patch, inflammation, chronic, suppurative | | 1 (2%) | | |
| Intestine small, ileum | (48) | (49) | (48) | (49) |
| Epithelium, cyst | 1 (2%) | | | |
| Peyer's patch, hyperplasia, lymphoid | | | | 3 (6%) |
| Liver | (50) | (50) | (50) | (50) |
| Basophilic focus | 4 (8%) | 5 (10%) | | 1 (2%) |
| Basophilic focus, multiple | 1 (2%) | | | 1 (2%) |
| Clear cell focus | 4 (8%) | 5 (10%) | 6 (12%) | 9 (18%) |
| Clear cell focus, multiple | | 1 (2%) | 1 (2%) | |
| Cyst | | 1 (2%) | | 1 (2%) |
| Eosinophilic focus | 3 (6%) | 3 (6%) | 2 (4%) | 6 (12%) |
| Infiltration cellular, mixed cell | 30 (60%) | 30 (60%) | 26 (52%) | 33 (66%) |
| Inflammation, chronic | 1 (2%) | | | |
| Mixed cell focus | 1 (2%) | 1 (2%) | 2 (4%) | 3 (6%) |
| Pigmentation, foal | | 1 (2%) | | |
| Thrombosis | 1 (2%) | | | |
| Bile duct, hyperplasia | | | 1 (2%) | 1 (2%) |
| Centrilobular, necrosis | | | 1 (2%) | |
| Hepatocyte, fatty change, diffuse | | 1 (2%) | | |
| Hepatocyte, necrosis, focal | 4 (8%) | 3 (6%) | 4 (8%) | 3 (6%) |
| Hepatocyte, syncytial alteration, focal | 2 (4%) | 13 (26%) | 17 (34%) | 33 (66%) |
| Hepatocyte, vacuolization cytoplasmic, diffuse | 1 (2%) | | | |
| Hepatocyte, vacuolization cytoplasmic, focal | 1 (2%) | | | 1 (2%) |
| Hepatocyte, centrilobular, fatty change | | 1 (2%) | | |
| Serosa, inflammation, chronic | | | 1 (2%) | |
| Mesentery | (6) | (7) | (8) | (5) |
| Hemorrhage | | | 1 (13%) | |
| Inflammation, chronic | 1 (17%) | 1 (14%) | 1 (13%) | 2 (40%) |
| Fat, necrosis | 4 (67%) | 4 (57%) | 4 (50%) | 2 (40%) |

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

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Alimentary System** (continued) | | | | |
| Oral mucosa | | | | (1) |
| Inflammation, chronic | | | | 1 (100%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Angiectasis | | | | 1 (2%) |
| Inflammation, chronic | | | 1 (2%) | |
| Lipomatosis | | | 1 (2%) | |
| Acinus, atrophy, diffuse | | | 1 (2%) | |
| Acinus, cytoplasmic alteration | | 1 (2%) | | |
| Duct, cyst | 1 (2%) | | 1 (2%) | |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Diverticulum | | | 1 (2%) | |
| Edema | | 1 (2%) | | |
| Inflammation, focal | 1 (2%) | 1 (2%) | | |
| Ulcer | | 1 (2%) | 1 (2%) | |
| Epithelium, cyst | | 1 (2%) | | |
| Epithelium, hyperplasia | 3 (6%) | 5 (10%) | | 2 (4%) |
| Stomach, glandular | (49) | (49) | (50) | (50) |
| Foreign body | | | | 1 (2%) |
| Inflammation, focal | | | | 1 (2%) |
| Pigmentation, focal | | | 1 (2%) | |
| Epithelium, cytoplasmic alteration, focal | | | | 1 (2%) |
| Glands, degeneration, cystic, focal | 1 (2%) | | | 1 (2%) |
| Tooth | (6) | (13) | (8) | (8) |
| Malformation | 1 (17%) | 1 (8%) | | 2 (25%) |
| Peridontal tissue, inflammation, chronic | 5 (83%) | 13 (100%) | 8 (100%) | 6 (75%) |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Infiltration cellular, mixed cell | 2 (4%) | 1 (2%) | 3 (6%) | 3 (6%) |
| Inflammation, chronic, focal | 2 (4%) | 1 (2%) | | |
| Mineralization | | | 1 (2%) | |
| **Endocrine System** | | | | |
| Adrenal cortex | (49) | (50) | (49) | (50) |
| Accessory adrenal cortical nodule | | 2 (4%) | | |
| Cyst | 1 (2%) | 1 (2%) | | |
| Cytoplasmic alteration, focal | 1 (2%) | 5 (10%) | 9 (18%) | 2 (4%) |
| Hypertrophy | | | | 1 (2%) |
| Hypertrophy, focal | 4 (8%) | | | 4 (8%) |
| Infiltration cellular, mixed cell | 1 (2%) | | | |
| Capsule, hyperplasia, focal | 1 (2%) | 6 (12%) | 1 (2%) | 1 (2%) |
| Adrenal medulla | (49) | (50) | (49) | (49) |
| Hyperplasia | | 1 (2%) | 1 (2%) | |
| Parathyroid gland | (48) | (45) | (44) | (50) |
| Cyst | | | | 3 (6%) |
| Pituitary gland | (46) | (49) | (49) | (45) |
| Pars distalis, cyst | 2 (4%) | 1 (2%) | 1 (2%) | |
| Pars distalis, hyperplasia, focal | | 1 (2%) | | |
| Pars intermedia, hyperplasia, focal | | | 1 (2%) | |
| Thyroid gland | (50) | (50) | (49) | (49) |
| Degeneration, cystic, focal | 10 (20%) | 9 (18%) | 13 (27%) | 15 (31%) |
| Follicle, cyst | | 1 (2%) | | |
| Follicular cell, hyperplasia | | 1 (2%) | | |

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Inflammation, chronic | | | 1 (2%) | 1 (2%) |
| Preputial gland | (50) | (50) | (50) | (50) |
| Degeneration, cystic | 29 (58%) | 29 (58%) | 32 (64%) | 28 (56%) |
| Inflammation, chronic | 3 (6%) | 2 (4%) | 1 (2%) | |
| Bilateral, degeneration, cystic | | 2 (4%) | | |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Dilatation | 1 (2%) | 1 (2%) | | |
| Inflammation, chronic | | 1 (2%) | | |
| Testes | (50) | (50) | (50) | (50) |
| Cyst | 1 (2%) | | | |
| Germinal epithelium, degeneration | | | 3 (6%) | 1 (2%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Angiectasis | | | | 1 (2%) |
| Hyperplasia | | | 1 (2%) | 1 (2%) |
| Hyperplasia, focal, histiocytic | | | | 1 (2%) |
| Inflammation, chronic, focal | 1 (2%) | | | |
| Necrosis, focal | | | | 1 (2%) |
| Lymph node | (5) | (5) | (3) | (5) |
| Bronchial, hyperplasia | 1 (20%) | | | |
| Bronchial, hyperplasia, lymphoid | | 1 (20%) | 1 (33%) | |
| Inguinal, hyperplasia, lymphoid | 1 (20%) | | | |
| Mediastinal, hyperplasia | | | | 1 (20%) |
| Mediastinal, hyperplasia, lymphoid | | 1 (20%) | | 1 (20%) |
| Mediastinal, infiltration cellular, lipocyte | | 1 (20%) | | |
| Mediastinal, pigmentation | 1 (20%) | | | |
| Pancreatic, amyloid deposition | | | | 1 (20%) |
| Pancreatic, hyperplasia | | | | 1 (20%) |
| Renal, hyperplasia | | | | 1 (20%) |
| Lymph node, mandibular | (48) | (50) | (45) | (48) |
| Hyperplasia | 1 (2%) | | | |
| Hyperplasia, lymphoid | 1 (2%) | | 1 (2%) | 1 (2%) |
| Lymph node, mesenteric | (50) | (49) | (49) | (49) |
| Hemorrhage | | 1 (2%) | | |
| Hyperplasia | | 1 (2%) | | 1 (2%) |
| Hyperplasia, lymphoid | | | | 1 (2%) |
| Inflammation, chronic, suppurative | | 1 (2%) | | |
| Spleen | (50) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | | |
| Congestion | 1 (2%) | 1 (2%) | | |
| Depletion cellular | 1 (2%) | | 1 (2%) | |
| Fibrosis, focal | 2 (4%) | | | |
| Hematopoietic cell proliferation | 9 (18%) | 15 (30%) | 10 (20%) | 11 (22%) |
| Hyperplasia, lymphoid | 3 (6%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Inflammation, focal | | | | 1 (2%) |

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Hematopoietic System** (continued) | | | | |
| Thymus | (47) | (40) | (44) | (45) |
| Atrophy | 1 (2%) | | | |
| Cyst | 3 (6%) | 3 (8%) | 1 (2%) | |
| Hyperplasia, lymphoid | 1 (2%) | | | 1 (2%) |
| Epithelial cell, hyperplasia | 1 (2%) | 1 (3%) | | |
| **Integumentary System** | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Subcutaneous tissue, edema | | | 1 (2%) | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Cranium, hyperostosis | 1 (2%) | | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Atrophy, focal | | 1 (2%) | | |
| Hemorrhage, focal | | 1 (2%) | | |
| Peripheral nerve | (1) | | | |
| Sciatic, degeneration | 1 (100%) | | | |
| Spinal cord | (2) | | | (1) |
| Meninges, inflammation, focal | 1 (50%) | | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | | 2 (4%) |
| Embolus | 1 (2%) | | | |
| Hemorrhage | | 7 (14%) | 4 (8%) | 1 (2%) |
| Hyperplasia, histiocytic | | 1 (2%) | 1 (2%) | 1 (2%) |
| Hyperplasia, lymphoid | | | | 1 (2%) |
| Infiltration cellular, mixed cell | | | | 2 (4%) |
| Thrombosis | | | 1 (2%) | |
| Alveolar epithelium, bronchiolization | | 20 (40%) | 30 (60%) | 48 (96%) |
| Alveolar epithelium, hyperplasia | 1 (2%) | 1 (2%) | 4 (8%) | 6 (12%) |
| Bronchiole, hyperplasia | | | | 1 (2%) |
| Mediastinum, inflammation, chronic | 1 (2%) | | | |
| Nose | (50) | (50) | (50) | (50) |
| Foreign body | | 1 (2%) | | |
| Inflammation, suppurative | 1 (2%) | 1 (2%) | | 1 (2%) |
| Nasolacrimal duct, cyst | | 1 (2%) | | |
| Nasolacrimal duct, inflammation | | 1 (2%) | | |
| Sinus, foreign body | 1 (2%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Sinus, inflammation, chronic, suppurative | 1 (2%) | 3 (6%) | 3 (6%) | 2 (4%) |
| **Special Senses System** | | | | |
| Eye | (1) | (1) | | |
| Cataract | 1 (100%) | | | |
| Cornea, inflammation, chronic | | 1 (100%) | | |
| Cornea, necrosis, focal | 1 (100%) | | | |

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Urinary System** | | | | |
| Kidney | (50) | (49) | (50) | (50) |
| Atrophy, focal | 1 (2%) | | | |
| Congestion | 2 (4%) | 2 (4%) | 2 (4%) | |
| Cyst | 2 (4%) | | 1 (2%) | |
| Cyst, multiple | 1 (2%) | | | |
| Inflammation, chronic | | 1 (2%) | | |
| Nephropathy | 46 (92%) | 49 (100%) | 47 (94%) | 43 (86%) |
| Nephropathy, focal | 1 (2%) | | | 1 (2%) |
| Glomerulus, thrombosis | | | 1 (2%) | |
| Pelvis, dilatation | | | 1 (2%) | |
| Renal tubule, accumulation, hyaline droplet | | | 1 (2%) | |
| Renal tubule, hyperplasia, focal | 1 (2%) | 1 (2%) | 2 (4%) | |
| Renal tubule, pigmentation | | | 1 (2%) | |

# APPENDIX D
# SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF *p*-NITROTOLUENE

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 1 | 5 | 1 |
| Natural deaths | 2 | 2 | 2 | |
| Survivors | | | | |
| Died last week of study | | | 2 | |
| Terminal sacrifice | 46 | 47 | 41 | 49 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Intestine small, duodenum | (49) | (49) | (49) | (50) |
| Adenocarcinoma | | | | 1 (2%) |
| Intestine small, jejunum | (49) | (48) | (48) | (50) |
| Carcinoma | | 1 (2%) | | |
| Liver | (49) | (50) | (50) | (50) |
| Hepatocellular carcinoma | 3 (6%) | 4 (8%) | | 1 (2%) |
| Hepatocellular adenoma | 6 (12%) | 3 (6%) | 2 (4%) | 4 (8%) |
| Hepatocellular adenoma, multiple | | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| Mesentery | (3) | (3) | (4) | (7) |
| Histiocytic sarcoma | | | 1 (25%) | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (25%) | |
| Pancreas | (49) | (50) | (49) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (49) | (50) | (50) | (50) |
| Squamous cell papilloma | | 3 (6%) | 2 (4%) | 1 (2%) |
| Tongue | | | (1) | |
| Squamous cell carcinoma | | | 1 (100%) | |
| **Cardiovascular System** | | | | |
| None | | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Capsule, sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Pheochromocytoma benign | | | 1 (2%) | |
| Pituitary gland | (45) | (49) | (49) | (45) |
| Pars distalis, adenoma | | 1 (2%) | 1 (2%) | |
| Pars intermedia, carcinoma | | | 1 (2%) | |
| Thyroid gland | (50) | (50) | (49) | (50) |
| Follicular cell, adenoma | | 1 (2%) | | |
| **General Body System** | | | | |
| None | | | | |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Genital System** | | | | |
| Ovary | (48) | (50) | (50) | (49) |
| Cystadenoma | 3 (6%) | 1 (2%) | 2 (4%) | |
| Granulosa cell tumor malignant | | | 1 (2%) | |
| Granulosa cell tumor benign | 1 (2%) | | | |
| Hemangioma | 1 (2%) | | | |
| Luteoma | | | 1 (2%) | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| Uterus | (50) | (50) | (50) | (50) |
| Leiomyoma | | 1 (2%) | 1 (2%) | |
| Leiomyosarcoma | | | | 1 (2%) |
| Cervix, hemangiosarcoma | | 1 (2%) | | |
| Endometrium, adenoma | | | 1 (2%) | |
| Endometrium, polyp stromal | 3 (6%) | 1 (2%) | 4 (8%) | 1 (2%) |
| Endometrium, sarcoma stromal | | | 1 (2%) | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Lymph node | (2) | (5) | (13) | (4) |
| Fibrosarcoma, metastatic, skin | | | 2 (15%) | |
| Bronchial, histiocytic sarcoma | | | 1 (8%) | |
| Iliac, histiocytic sarcoma | | | 1 (8%) | |
| Iliac, sarcoma, metastatic, skeletal muscle | | | 1 (8%) | |
| Inguinal, fibrosarcoma, metastatic, skin | | | 1 (8%) | |
| Inguinal, histiocytic sarcoma | | | 1 (8%) | |
| Mediastinal, sarcoma, metastatic, skeletal muscle | | | 1 (8%) | |
| Pancreatic, histiocytic sarcoma | | | 1 (8%) | |
| Renal, histiocytic sarcoma | | | 1 (8%) | |
| Lymph node, mandibular | (50) | (48) | (48) | (47) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Lymph node, mesenteric | (48) | (49) | (49) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Spleen | (49) | (50) | (49) | (50) |
| Hemangiosarcoma | | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Thymus | (48) | (49) | (47) | (46) |
| Histiocytic sarcoma | | | 1 (2%) | |
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Carcinoma | | | 1 (2%) | |
| Skin | (50) | (50) | (50) | (50) |
| Squamous cell carcinoma | | | 1 (2%) | |
| Subcutaneous tissue, fibrosarcoma | 1 (2%) | | 4 (8%) | |
| Subcutaneous tissue, hemangiosarcoma | 1 (2%) | | | |
| Subcutaneous tissue, lipoma | 1 (2%) | | | |
| Subcutaneous tissue, sarcoma | 1 (2%) | | | |
| Subcutaneous tissue, sarcoma NOS, metastatic skin | | | 1 (2%) | |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Musculoskeletal System** | | | | |
| Skeletal muscle | (1) | | (3) | (1) |
| Sarcoma NOS, metastatic, skeletal muscle | | | 2 (67%) | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pituitary gland | | | 1 (2%) | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 5 (10%) | 2 (4%) | 2 (4%) | 5 (10%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | | 2 (4%) | 3 (6%) |
| Fibrosarcoma, metastatic, skin | | | 2 (4%) | |
| Hepatocellular carcinoma, metastatic, liver | | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| Serosa, sarcoma, metastatic, skeletal muscle | | | 1 (2%) | |
| **Special Senses System** | | | | |
| Ear | | (1) | | |
| External ear, melanoma malignant | | 1 (100%) | | |
| Harderian gland | (2) | (3) | (2) | (3) |
| Adenoma | 2 (100%) | 2 (67%) | 1 (50%) | 3 (100%) |
| Carcinoma | | 1 (33%) | 1 (50%) | |
| **Urinary System** | | | | |
| Kidney | (49) | (50) | (50) | (50) |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Lymphoma malignant | 3 (6%) | 5 (10%) | 9 (18%) | 5 (10%) |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | 21 | 23 | 29 | 25 |
| Total primary neoplasms | 32 | 28 | 41 | 27 |
| Total animals with benign neoplasms | 17 | 14 | 14 | 14 |
| Total benign neoplasms | 22 | 15 | 18 | 15 |
| Total animals with malignant neoplasms | 9 | 13 | 21 | 12 |
| Total malignant neoplasms | 10 | 13 | 23 | 12 |
| Total animals with metastatic neoplasms | | | 7 | 1 |
| Total metastatic neoplasms | | | 18 | 1 |

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

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 6 2 9 | 6 5 4 | 6 8 2 | 7 0 7 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 5 0 | 2 3 9 | 2 2 0 | 2 2 5 | 2 2 1 | 2 2 2 | 2 2 3 | 2 2 4 | 2 3 1 | 2 3 2 | 2 3 3 | 2 3 4 | 2 3 5 | 2 4 6 | 2 4 7 | 2 4 8 | 2 4 9 | 2 0 1 | 2 0 2 | 2 0 3 | 2 0 4 | 2 0 5 | 2 1 1 | 2 1 2 | 2 1 3 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | X | | | | | | | | X | | | | | | X | | | | | | | | | | |
| Mesentery | | + | | | | | | + | | | | | | | | | | | | | | | | | | |
| Pancreas | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | + | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | M | M | + | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endometrium, polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | | |

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

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 1 4 | 2 1 5 | 2 1 6 | 2 1 7 | 2 1 8 | 2 1 9 | 2 2 6 | 2 2 7 | 2 2 8 | 2 2 9 | 2 3 0 | 2 0 6 | 2 0 7 | 2 0 8 | 2 0 9 | 2 1 0 | 2 3 6 | 2 3 7 | 2 3 8 | 2 4 0 | 2 4 1 | 2 4 2 | 2 4 3 | 2 4 4 | 2 4 5 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hepatocellular carcinoma | X | | | | | X | | | | | | X | | | | | | | | | | | | | | 3 |
| Hepatocellular adenoma | | | | | | | | | | | | X | | | | | | | | X | | | | | X | 6 |
| Mesentery | | | + | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Tooth | | | | | | | | | | + | | | | | | | | | | | + | | | | | 3 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | | | | | + | | | | | | | | | | | | | | | | | | | | 1 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 49 |
| Pituitary gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | 45 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | 48 |
| Cystadenoma | | | | | | | | | | | X | | X | | | | | | | | | | | | | 3 |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endometrium, polyp stromal | | | | | | | X | | | | | | | X | | | | | | X | | | | | | 3 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 629 | 654 | 682 | 707 | 733 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 25010 | 23209 | 22200 | 22255 | 22211 | 22212 | 22223 | 22234 | 23231 | 23312 | 23323 | 23334 | 23345 | 24466 | 24477 | 24488 | 24499 | 00101 | 00202 | 00303 | 00404 | 00505 | 01121 | 01122 | 01123 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | + | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | A | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, fibrosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, hemangiosarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | | | | | | | | | | | X | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | X | | | | X | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 0 ppm**

| Number of Days on Study | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 1 4 | 2 1 5 | 2 1 6 | 2 1 7 | 2 1 8 | 2 1 9 | 2 2 6 | 2 2 7 | 2 2 8 | 2 2 9 | 2 3 0 | 2 0 6 | 2 0 7 | 2 0 8 | 2 0 9 | 2 1 0 | 2 3 6 | 2 3 7 | 2 3 8 | 2 4 0 | 2 4 1 | 2 4 2 | 2 4 3 | 2 4 4 | 2 4 5 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | | | | | | | | | + | | | | | | | 2 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | 48 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, lipoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | X | | | | | | | | | | | | | | | | X | | | | | | | X | 5 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | + | | | | | | | | | | | + | | | | | | | | | | | | | | 2 |
| Adenoma | X | | | | | | | | | | | X | | | | | | | | | | | | | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | X | | | | | | 3 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 4 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 | 6 | 8 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 7 | 4 | 0 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 5 | 5 | 5 | 5 |
| **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 |
| | 5 | 8 | 8 | 8 | 8 | 8 | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 9 | 9 | 9 | 9 | 9 | 6 | 6 | 6 | 6 |
| | 3 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Intestine small, ileum | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | X | | | | X | | | | | | | | | | | | | | X | | | | | | |
| Hepatocellular adenoma | | | | | X | | | | | | | | | | | X | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | + | | | | | | | + | | | | | | | | | | | + | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | M | + | + | M |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cervix, hemangiosarcoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Endometrium, polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 735 | 735 | 735 | 735 | 735 | 735 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 27 70 | 27 71 | 27 72 | 27 73 | 27 74 | 27 75 | 26 61 | 26 62 | 26 63 | 26 64 | 26 65 | 27 76 | 27 77 | 27 78 | 27 79 | 28 00 | 28 01 | 28 02 | 28 03 | 28 04 | 29 06 | 29 07 | 29 08 | 29 09 | 30 00 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, rectum | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 4 |
| Hepatocellular adenoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Mesentery | | | + | | | | | | | | + | | | | | + | | | | | | | | | | 3 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | X | | | | | | | | | | | | | | | | X | | | X | 3 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tooth | | | | | | | | | | | | + | | | | | | | | + | + | | | | | 6 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | 49 |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Follicular cell, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Cervix, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Endometrium, polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 4 8 7 | 6 6 4 | 6 8 0 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 5 | 7 3 5 | 7 3 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 5 3 | 2 8 5 | 2 8 6 | 2 8 7 | 2 8 8 | 2 8 9 | 2 9 0 | 2 5 1 | 2 5 2 | 2 5 4 | 2 5 5 | 2 5 6 | 2 5 7 | 2 5 8 | 2 5 9 | 2 6 0 | 2 9 1 | 2 9 2 | 2 9 3 | 2 9 4 | 2 9 5 | 2 6 6 | 2 6 7 | 2 6 8 | 2 6 9 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | | | | | | | | | | | | | | + | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | |
| External ear, melanoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | + | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | X | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 1,250 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 7 0 | 2 7 1 | 2 7 2 | 2 7 3 | 2 7 4 | 2 7 5 | 2 6 1 | 2 6 2 | 2 6 3 | 2 6 4 | 2 6 5 | 2 6 6 | 2 7 7 | 2 7 8 | 2 7 9 | 2 8 0 | 2 8 1 | 2 8 2 | 2 8 3 | 2 8 4 | 2 9 6 | 2 9 7 | 2 9 8 | 2 9 9 | 3 0 0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | + | | | | | | | | + | | | | | | | + | | | | | | | | | | 5 |
| Lymph node, mandibular | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | | | | 2 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | + | | | | | | | | | | | | | | | | | | | | | | | 1 |
| External ear, melanoma malignant | | | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | + | | | | | | | | | | | | | + | | | | | | | | | | | 3 |
| Adenoma | | | | X | | | | | | | | | | | | | X | | | | | | | | | | | 2 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant | | | X | | | | | | | X | X | | | | | | X | | | | | | | | | | | 5 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 4 5 6 | 5 3 4 | 6 2 5 | 6 6 9 | 6 8 2 | 7 1 4 | 7 1 6 | 7 3 0 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 8 | 3 4 9 | 3 1 5 | 3 2 3 | 3 1 8 | 3 4 6 | 3 1 0 | 3 3 0 | 3 2 6 | 3 2 7 | 3 2 8 | 3 2 9 | 3 3 4 | 3 0 6 | 3 0 7 | 3 0 8 | 3 0 9 | 3 1 1 | 3 1 2 | 3 1 3 | 3 1 4 | 3 2 1 | 3 2 2 | 3 2 4 | 3 2 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | M | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | A | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | + | + | | | | | | | | | | | | + | | | + | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | X | | | | X | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | | | + | | + | | + | | + | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | M | + | + | + |
| Pituitary gland | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars intermedia, carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 735 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | 736 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 30 01 | 30 02 | 30 03 | 30 04 | 30 05 | 30 31 | 30 32 | 30 33 | 30 35 | 30 36 | 30 37 | 30 39 | 30 40 | 30 47 | 30 48 | 30 50 | 30 16 | 30 17 | 30 19 | 30 20 | 30 41 | 30 42 | 30 43 | 30 44 | 30 45 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Tongue | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 |
| Squamous cell carcinoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Tooth | | | | | | + | + | | | | | | | | + | | | | | | | | | | | 7 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | M | M | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | 44 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Pars intermedia, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 4 5 6 | 5 3 4 | 6 2 5 | 6 6 9 | 6 8 2 | 7 1 4 | 7 1 6 | 7 3 0 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 8 | 3 4 9 | 3 1 5 | 3 2 3 | 3 1 8 | 3 4 6 | 3 1 0 | 3 3 0 | 3 2 6 | 3 2 7 | 3 2 8 | 3 2 9 | 3 3 4 | 3 3 6 | 3 3 7 | 3 3 8 | 3 3 9 | 3 1 1 | 3 1 2 | 3 1 3 | 3 1 4 | 3 2 1 | 3 2 2 | 3 2 4 | 3 2 5 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | X | X | | | | | | | | | | |
| Granulosa cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Luteoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Endometrium, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endometrium, polyp stromal | | | | | | | | | | | | | | | X | X | X | | | | | | | | |
| Endometrium, sarcoma stromal | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph node | + | | | | + | | + | + | | + | + | | | + | | | | | + | + | | | + | | |
| Fibrosarcoma, metastatic, skin | X | | | | X | | | | | | | | | | | | | | | | | | | | |
| Bronchial, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Iliac, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Iliac, sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Inguinal, fibrosarcoma, metastatic, skin | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Inguinal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Mediastinal, sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Renal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Spleen | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Thymus | + | + | + | I | + | + | I | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Subcutaneous tissue, fibrosarcoma | X | X | | X | X | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma NOS, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | + | + | | | | | | | | | | | | | | | | | | |
| Sarcoma NOS, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 0 1 | 3 0 2 | 3 0 3 | 3 0 4 | 3 0 5 | 3 3 1 | 3 3 2 | 3 3 3 | 3 3 5 | 3 3 6 | 3 3 7 | 3 3 9 | 3 4 0 | 3 4 7 | 3 4 8 | 3 5 0 | 3 1 6 | 3 1 7 | 3 1 9 | 3 2 0 | 3 4 1 | 3 4 2 | 3 4 3 | 3 4 4 | 3 4 5 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Granulosa cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Luteoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Endometrium, adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Endometrium, polyp stromal | | | | | | | | | | X | | | | | | | | | | | | | | | | | | 4 |
| Endometrium, sarcoma stromal | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | | | | | + | | | | | | | | | + | | | | | + | | | | | | | | 13 |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Bronchial, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Iliac, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Iliac, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Inguinal, fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Inguinal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinal, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Renal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Subcutaneous tissue, sarcoma NOS, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | + | | | | | | | | | | | | 3 |
| Sarcoma NOS, metastatic, skeletal muscle | | | | | | | | | | | | | | | | X | | | | | | | | | | | | 2 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 4 5 6 | 5 3 4 | 6 2 5 | 6 6 9 | 6 8 2 | 7 1 4 | 7 1 6 | 7 3 0 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 8 | 3 4 9 | 3 1 5 | 3 2 3 | 3 1 8 | 3 4 6 | 3 1 0 | 3 3 0 | 3 2 6 | 3 2 7 | 3 2 8 | 3 2 9 | 3 3 4 | 3 0 6 | 3 0 7 | 3 0 8 | 3 0 9 | 3 1 1 | 3 1 2 | 3 1 3 | 3 1 4 | 3 2 1 | 3 2 2 | 3 2 4 | 3 2 5 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pituitary gland | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Peripheral nerve | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | + | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | | | | | X | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | X | | | | | | | | X | | | | | | |
| Fibrosarcoma, metastatic, skin | | | | X | X | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Sarcoma, metastatic, skeletal muscle | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Serosa, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | + | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymphoma malignant | | | | | | | | X | | | | | | X | X | | | | | | | X | X | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 2,500 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 0 1 | 3 0 2 | 3 0 3 | 3 0 4 | 3 0 5 | 3 3 1 | 3 3 2 | 3 3 3 | 3 3 5 | 3 3 6 | 3 3 7 | 3 3 9 | 3 4 0 | 3 4 7 | 3 4 8 | 3 5 0 | 3 1 6 | 3 1 7 | 3 1 9 | 3 2 0 | 3 4 1 | 3 4 2 | 3 4 3 | 3 4 4 | 3 4 5 | Total Tissues/ Tumors |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Serosa, sarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | | | | | + | | | | | | | | | | | + | | | | | | | | 2 |
| Adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant | | X | | | | X | | | | | | | | | X | | | | | X | | | | | | | 9 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 27 26 | 72 99 | 72 99 | 72 99 | 72 99 | 72 99 | 73 32 | 73 32 | 73 32 | 73 32 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 36 61 | 36 66 | 36 67 | 36 68 | 36 69 | 37 00 | 36 62 | 36 63 | 36 64 | 36 65 | 35 51 | 55 12 | 55 23 | 55 34 | 55 45 | 58 11 | 58 22 | 58 33 | 58 44 | 58 55 | 59 11 | 59 22 | 59 33 | 59 44 | 59 55 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | X | | | | X | | | X | | | | | | | | | | | | | X | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | + | | | | + | + | | | | | | + | | | | + | | | | | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | + | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | M | + | + | + | + | + | M | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | M |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | + | | | | | | | | | + |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endometrium, polyp stromal | | | X | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 5 6 | 3 5 5 7 | 3 5 5 8 | 3 5 5 9 | 3 6 0 | 3 7 1 | 3 7 2 | 3 7 3 | 3 7 4 | 3 7 5 | 3 8 6 | 3 8 7 | 3 8 8 | 3 8 9 | 3 9 0 | 3 7 6 | 3 7 7 | 3 7 8 | 3 7 9 | 3 8 0 | 3 9 6 | 3 9 7 | 3 9 8 | 3 9 9 | 4 0 0 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Hepatocellular adenoma, multiple | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | + | | | | | | | | | 7 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tooth | | | | | | | | + | + | + | + | | | | | | | | | | | | | + | | 6 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + | + | 48 |
| Pituitary gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peritoneum | | | | | | | | | | | | | | | | | | | + | | | | | | | 1 |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Ovary | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Endometrium, polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 27 36 | 72 99 | 72 99 | 72 99 | 72 99 | 72 99 | 73 02 | 73 22 | 73 32 | 73 32 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 | 73 33 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 36 61 | 36 66 | 36 67 | 36 68 | 36 69 | 37 00 | 36 02 | 36 63 | 36 64 | 36 65 | 35 51 | 35 52 | 35 53 | 35 54 | 35 55 | 38 81 | 38 82 | 38 83 | 38 84 | 38 85 | 39 01 | 39 02 | 39 03 | 39 04 | 39 05 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | + | | | | | | | | | + | | | | | | | | | | + | |
| Lymph node, mandibular | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | + | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | + | | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | + | | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | X | | | X | | |
| Alveolar/bronchiolar carcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lacrimal gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | X | | | | X | X | | | | | | | | | X | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene: 5,000 ppm**

| Number of Days on Study | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 5 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 5 5 6 | 3 5 5 7 | 3 5 5 8 | 3 5 5 9 | 3 5 6 0 | 3 5 7 1 | 3 5 7 2 | 3 5 7 3 | 3 5 7 4 | 3 5 7 5 | 3 5 8 6 | 3 5 8 7 | 3 5 8 8 | 3 5 8 9 | 3 5 9 0 | 3 5 7 6 | 3 5 7 7 | 3 5 7 8 | 3 5 7 9 | 3 5 8 0 | 3 5 9 6 | 3 5 9 7 | 3 5 9 8 | 3 5 9 9 | 4 0 0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | + | | 4 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Thymus | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | X | | | | | | | | | | | | | | | | | X | | | | | | | X | 5 |
| Alveolar/bronchiolar carcinoma | | | | | | | X | | | | X | | | | | | | | | | | | | | | 3 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | + | | | | | | + | | | | | + | | | | | 3 |
| Adenoma | | | | | | | | | | X | | | | | | X | | | | | X | | | | | 3 |
| Lacrimal gland | | | | | | + | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | X | | 5 |

**TABLE D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Harderian Gland: Adenoma** | | | | |
| Overall rate[a] | 2/50 (4%) | 2/50 (4%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate[b] | 4.1% | 4.1% | 2.1% | 6.1% |
| Terminal rate[c] | 2/46 (4%) | 2/47 (4%) | 1/43 (2%) | 3/49 (6%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test[d] | P=0.403 | P=0.692 | P=0.510N | P=0.500 |
| **Harderian Gland: Adenoma or Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 3/50 (6%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 4.1% | 6.1% | 4.2% | 6.1% |
| Terminal rate | 2/46 (4%) | 3/47 (6%) | 2/43 (5%) | 3/49 (6%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.455 | P=0.498 | P=0.683 | P=0.500 |
| **Liver: Hepatocellular Adenoma** | | | | |
| Overall rate | 6/49 (12%) | 3/50 (6%) | 2/50 (4%) | 5/50 (10%) |
| Adjusted rate | 12.3% | 6.1% | 4.2% | 10.2% |
| Terminal rate | 5/46 (11%) | 3/47 (6%) | 2/43 (5%) | 5/49 (10%) |
| First incidence (days) | 654 | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.495N | P=0.242N | P=0.140N | P=0.495N |
| **Liver: Hepatocellular Carcinoma** | | | | |
| Overall rate | 3/49 (6%) | 4/50 (8%) | 0/50 (0%) | 1/50 (2%) |
| Adjusted rate | 6.2% | 8.1% | 0.0% | 2.0% |
| Terminal rate | 3/46 (7%) | 3/47 (6%) | 0/43 (0%) | 1/49 (2%) |
| First incidence (days) | 729 (T) | 487 | —[e] | 729 (T) |
| Poly-3 test | P=0.110N | P=0.512 | P=0.122N | P=0.301N |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | | |
| Overall rate | 8/49 (16%) | 6/50 (12%) | 2/50 (4%) | 6/50 (12%) |
| Adjusted rate | 16.4% | 12.1% | 4.2% | 12.2% |
| Terminal rate | 7/46 (15%) | 5/47 (11%) | 2/43 (5%) | 6/49 (12%) |
| First incidence (days) | 654 | 487 | 729 (T) | 729 (T) |
| Poly-3 test | P=0.296N | P=0.374N | P=0.049N | P=0.382N |
| **Lung: Alveolar/bronchiolar Adenoma** | | | | |
| Overall rate | 5/50 (10%) | 2/50 (4%) | 2/50 (4%) | 5/50 (10%) |
| Adjusted rate | 10.2% | 4.1% | 4.2% | 10.2% |
| Terminal rate | 5/46 (11%) | 2/47 (4%) | 1/43 (2%) | 5/49 (10%) |
| First incidence (days) | 729 (T) | 729 (T) | 714 | 729 (T) |
| Poly-3 test | P=0.461 | P=0.219N | P=0.228N | P=0.629 |
| **Lung: Alveolar/bronchiolar Carcinoma** | | | | |
| Overall rate | 1/50 (2%) | 0/50 (0%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 2.0% | 0.0% | 4.2% | 6.1% |
| Terminal rate | 1/46 (2%) | 0/47 (0%) | 2/43 (5%) | 3/49 (6%) |
| First incidence (days) | 729 (T) | — | 729 (T) | 729 (T) |
| Poly-3 test | P=0.104 | P=0.501N | P=0.490 | P=0.305 |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | | |
| Overall rate | 6/50 (12%) | 2/50 (4%) | 4/50 (8%) | 8/50 (16%) |
| Adjusted rate | 12.2% | 4.1% | 8.4% | 16.3% |
| Terminal rate | 6/46 (13%) | 2/47 (4%) | 3/43 (7%) | 8/49 (16%) |
| First incidence (days) | 729 (T) | 729 (T) | 714 | 729 (T) |
| Poly-3 test | P=0.168 | P=0.135N | P=0.387N | P=0.387 |

**TABLE D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Ovary: Cystadenoma** | | | | |
| Overall rate | 3/48 (6%) | 1/50 (2%) | 2/50 (4%) | 0/49 (0%) |
| Adjusted rate | 6.3% | 2.0% | 4.2% | 0.0% |
| Terminal rate | 3/45 (7%) | 1/47 (2%) | 2/43 (5%) | 0/48 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | — |
| Poly-3 test | P=0.101N | P=0.295N | P=0.497N | P=0.117N |
| **Skin (Subcutaneous Tissue): Fibrosarcoma** | | | | |
| Overall rate | 1/50 (2%) | 0/50 (0%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted rate | 2.0% | 0.0% | 8.1% | 0.0% |
| Terminal rate | 0/46 (0%) | 0/47 (0%) | 0/43 (0%) | 0/49 (0%) |
| First incidence (days) | 682 | — | 456 | — |
| Poly-3 test | P=0.532N | P=0.502N | P=0.181 | P=0.501N |
| **Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma** | | | | |
| Overall rate | 2/50 (4%) | 0/50 (0%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted rate | 4.1% | 0.0% | 8.1% | 0.0% |
| Terminal rate | 1/46 (2%) | 0/47 (0%) | 0/43 (0%) | 0/49 (0%) |
| First incidence (days) | 682 | — | 456 | — |
| Poly-3 test | P=0.336N | P=0.239N | P=0.340 | P=0.238N |
| **Stomach (Forestomach): Squamous Cell Papilloma** | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 2/50 (4%) | 1/50 (2%) |
| Adjusted rate | 0.0% | 6.1% | 4.2% | 2.0% |
| Terminal rate | 0/46 (0%) | 3/47 (6%) | 1/43 (2%) | 1/49 (2%) |
| First incidence (days) | — | 729 (T) | 682 | 729 (T) |
| Poly-3 test | P=0.555 | P=0.118 | P=0.232 | P=0.500 |
| **Uterus: Stromal Polyp or Stromal Sarcoma** | | | | |
| Overall rate | 3/50 (6%) | 1/50 (2%) | 4/50 (8%) | 1/50 (2%) |
| Adjusted rate | 6.1% | 2.0% | 8.4% | 2.0% |
| Terminal rate | 3/46 (7%) | 1/47 (2%) | 4/43 (9%) | 1/49 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.343N | P=0.307N | P=0.485 | P=0.306N |
| **All Organs: Malignant Lymphoma** | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 9/50 (18%) | 5/50 (10%) |
| Adjusted rate | 6.1% | 10.2% | 18.8% | 10.2% |
| Terminal rate | 2/46 (4%) | 4/47 (9%) | 9/43 (21%) | 5/49 (10%) |
| First incidence (days) | 707 | 680 | 729 (T) | 729 (T) |
| Poly-3 test | P=0.294 | P=0.356 | P=0.053 | P=0.356 |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 17/50 (34%) | 14/50 (28%) | 14/50 (28%) | 14/50 (28%) |
| Adjusted rate | 34.4% | 28.7% | 29.2% | 28.5% |
| Terminal rate | 16/46 (35%) | 14/47 (30%) | 12/43 (28%) | 14/49 (29%) |
| First incidence (days) | 654 | 729 (T) | 682 | 729 (T) |
| Poly-3 test | P=0.336N | P=0.346N | P=0.368N | P=0.341N |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 9/50 (18%) | 13/50 (26%) | 23/50 (46%) | 12/50 (24%) |
| Adjusted rate | 18.2% | 26.1% | 46.1% | 24.5% |
| Terminal rate | 7/46 (15%) | 11/47 (23%) | 17/43 (40%) | 12/49 (25%) |
| First incidence (days) | 682 | 487 | 456 | 729 (T) |
| Poly-3 test | P=0.238 | P=0.242 | P=0.002 | P=0.307 |

**TABLE D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 21/50 (42%) | 23/50 (46%) | 31/50 (62%) | 25/50 (50%) |
| Adjusted rate | 42.3% | 46.2% | 62.0% | 51.0% |
| Terminal rate | 18/46 (39%) | 21/47 (45%) | 24/43 (56%) | 25/49 (51%) |
| First incidence (days) | 654 | 487 | 456 | 729 (T) |
| Poly-3 test | P=0.174 | P=0.425 | P=0.037 | P=0.256 |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and ovary; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

**TABLE D4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 1 | 5 | 1 |
| Natural deaths | 2 | 2 | 2 | |
| Survivors | | | | |
| Died last week of study | | | 2 | |
| Terminal sacrifice | 46 | 47 | 41 | 49 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| **Alimentary System** | | | | |
| Gallbladder | (49) | (48) | (48) | (49) |
| Inflammation, chronic | | | | 1 (2%) |
| Intestine small, duodenum | (49) | (49) | (49) | (50) |
| Inflammation, chronic, focal | | | | 1 (2%) |
| Epithelium, cyst | | 1 (2%) | | |
| Intestine small, jejunum | (49) | (48) | (48) | (50) |
| Inflammation, focal | | | 1 (2%) | |
| Peyer's patch, hyperplasia, lymphoid | 1 (2%) | | | |
| Serosa, cyst | | 1 (2%) | | |
| Intestine small, ileum | (49) | (48) | (48) | (50) |
| Peyer's patch, hyperplasia, lymphoid | 2 (4%) | | | |
| Liver | (49) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | | |
| Atrophy, focal | | | | 1 (2%) |
| Basophilic focus | 2 (4%) | 3 (6%) | | |
| Congestion, focal | | | | 1 (2%) |
| Eosinophilic focus | | 3 (6%) | | |
| Hemorrhage, focal | | | | 1 (2%) |
| Hyperplasia, focal, lymphoid | 1 (2%) | 1 (2%) | 1 (2%) | |
| Infarct | | 1 (2%) | | |
| Infiltration cellular, mixed cell | 40 (82%) | 41 (82%) | 39 (78%) | 39 (78%) |
| Inflammation, chronic | 1 (2%) | 1 (2%) | | 1 (2%) |
| Mixed cell focus | | 1 (2%) | | |
| Tension lipidosis | | 1 (2%) | | |
| Artery, inflammation, chronic | | | | 1 (2%) |
| Bile duct, cyst | | | 1 (2%) | |
| Centrilobular, necrosis | | | 1 (2%) | |
| Hepatocyte, fatty change, diffuse | | | 1 (2%) | |
| Hepatocyte, necrosis, focal | | 2 (4%) | | 1 (2%) |
| Hepatocyte, vacuolization cytoplasmic, focal | | 1 (2%) | | |
| Hepatocyte, periportal, vacuolization cytoplasmic | | | | 3 (6%) |
| Portal, inflammation, chronic | | | | 1 (2%) |
| Serosa, inflammation, chronic | | | | 1 (2%) |
| Mesentery | (3) | (3) | (4) | (7) |
| Inflammation, chronic | | 2 (67%) | 1 (25%) | 1 (14%) |
| Artery, inflammation, chronic | 1 (33%) | | | 1 (14%) |
| Fat, necrosis | 1 (33%) | 1 (33%) | 1 (25%) | 1 (14%) |
| Pancreas | (49) | (50) | (49) | (50) |
| Acinus, atrophy, diffuse | 2 (4%) | | | |
| Acinus, atrophy, focal | 1 (2%) | | | 1 (2%) |
| Duct, cyst | 3 (6%) | | 1 (2%) | |

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

**TABLE D4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Alimentary System** (continued) | | | | |
| Stomach, forestomach | (49) | (50) | (50) | (50) |
| Diverticulum | | 5 (10%) | 1 (2%) | |
| Epithelium, hyperplasia | | 2 (4%) | | |
| Stomach, glandular | (49) | (50) | (49) | (50) |
| Erosion | | 1 (2%) | | |
| Tooth | (3) | (6) | (7) | (6) |
| Malformation | | | 1 (14%) | |
| Peridontal tissue, inflammation, chronic | 3 (100%) | 6 (100%) | 6 (86%) | 6 (100%) |
| **Cardiovascular System** | | | | |
| Blood vessel | (1) | | | |
| Inflammation, chronic | 1 (100%) | | | |
| Heart | (50) | (50) | (50) | (50) |
| Infiltration cellular, mixed cell | 4 (8%) | 2 (4%) | 1 (2%) | 6 (12%) |
| Inflammation, chronic, focal | 1 (2%) | | | |
| Artery, inflammation, chronic | 1 (2%) | | 1 (2%) | 1 (2%) |
| Epicardium, infiltration cellular, mixed cell | 2 (4%) | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Accessory adrenal cortical nodule | | 1 (2%) | | |
| Cyst | 1 (2%) | | | 1 (2%) |
| Cytoplasmic alteration, focal | | 1 (2%) | | |
| Hemorrhage | | | 1 (2%) | |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Hyperplasia | 1 (2%) | | | |
| Parathyroid gland | (49) | (48) | (44) | (48) |
| Cyst | | | 1 (2%) | |
| Pituitary gland | (45) | (49) | (49) | (45) |
| Angiectasis | | 1 (2%) | | |
| Pars distalis, angiectasis | | 1 (2%) | | |
| Pars distalis, cyst | | | 1 (2%) | |
| Pars distalis, cytoplasmic alteration, focal | 4 (9%) | 2 (4%) | 3 (6%) | |
| Pars distalis, hyperplasia, focal | | 2 (4%) | | |
| Thyroid gland | (50) | (50) | (49) | (50) |
| Degeneration, cystic, focal | 18 (36%) | 27 (54%) | 29 (59%) | 22 (44%) |
| Follicle, cyst | 1 (2%) | 1 (2%) | 1 (2%) | |
| Follicular cell, hyperplasia | 1 (2%) | 3 (6%) | 1 (2%) | |
| **General Body System** | | | | |
| Tissue NOS | | | | (2) |
| Abdominal, inflammation, chronic | | | | 1 (50%) |

**TABLE D4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Genital System** | | | | |
| Clitoral gland | (50) | (45) | (49) | (48) |
| Degeneration, cystic | 1 (2%) | | 2 (4%) | |
| Inflammation, chronic | | 1 (2%) | | |
| Pigmentation | 1 (2%) | 4 (9%) | 3 (6%) | 2 (4%) |
| Ovary | (48) | (50) | (50) | (49) |
| Angiectasis | 1 (2%) | 2 (4%) | | |
| Cyst | 11 (23%) | 13 (26%) | 13 (26%) | 13 (27%) |
| Cyst, multiple | | 1 (2%) | | |
| Hemorrhage | 1 (2%) | 2 (4%) | 5 (10%) | |
| Mineralization | 1 (2%) | | | |
| Bilateral, cyst | 1 (2%) | | | |
| Periovarian tissue, cyst | 1 (2%) | | | |
| Uterus | (50) | (50) | (50) | (50) |
| Angiectasis | | 1 (2%) | | |
| Cyst | 1 (2%) | | 4 (8%) | 3 (6%) |
| Hemorrhage | 2 (4%) | | | 1 (2%) |
| Hydrometra | 19 (38%) | 21 (42%) | 23 (46%) | 25 (50%) |
| Inflammation, suppurative | 1 (2%) | | | |
| Thrombosis | | 1 (2%) | | |
| Endometrium, hyperplasia, cystic | 47 (94%) | 45 (90%) | 44 (88%) | 49 (98%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hyperplasia | 1 (2%) | 1 (2%) | | |
| Hyperplasia, focal, histiocytic | | | | 1 (2%) |
| Lymph node | (2) | (5) | (13) | (4) |
| Bronchial, hyperplasia | | 1 (20%) | 2 (15%) | |
| Bronchial, hyperplasia, lymphoid | | | 3 (23%) | 1 (25%) |
| Iliac, hyperplasia, lymphoid | 1 (50%) | | | |
| Inguinal, hyperplasia, histiocytic | | | 1 (8%) | |
| Inguinal, hyperplasia, lymphoid | | | 1 (8%) | |
| Inguinal, pigmentation | | | | 1 (25%) |
| Mediastinal, hyperplasia, lymphoid | | | | 1 (25%) |
| Pancreatic, hyperplasia, lymphoid | | 1 (20%) | | |
| Renal, hyperplasia, lymphoid | 1 (50%) | 1 (20%) | | |
| Lymph node, mandibular | (50) | (48) | (48) | (47) |
| Hyperplasia | 1 (2%) | | | |
| Hyperplasia, lymphoid | | 1 (2%) | 2 (4%) | |
| Lymph node, mesenteric | (48) | (49) | (49) | (50) |
| Hyperplasia | | | 1 (2%) | 2 (4%) |
| Hyperplasia, histiocytic | | 1 (2%) | 1 (2%) | |
| Hyperplasia, lymphoid | 2 (4%) | 5 (10%) | | |
| Spleen | (49) | (50) | (49) | (50) |
| Congestion | | 1 (2%) | | |
| Hematopoietic cell proliferation | 2 (4%) | 7 (14%) | 11 (22%) | 4 (8%) |
| Hyperplasia, lymphoid | 5 (10%) | 9 (18%) | 4 (8%) | 2 (4%) |
| Thymus | (48) | (49) | (47) | (46) |
| Angiectasis | 1 (2%) | 2 (4%) | | |
| Cyst | 1 (2%) | 1 (2%) | 2 (4%) | |
| Hyperplasia, lymphoid | | | 2 (4%) | |

**TABLE D4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Ectasia | | | 2 (4%) | |
| Hyperplasia | | | 1 (2%) | |
| Skin | (50) | (50) | (50) | (50) |
| Subcutaneous tissue, angiectasis, focal | | | 1 (2%) | |
| Subcutaneous tissue, cyst epithelial inclusion | 1 (2%) | | | |
| Subcutaneous tissue, degeneration, mucoid | 1 (2%) | 1 (2%) | | |
| Subcutaneous tissue, edema | | 1 (2%) | | |
| Subcutaneous tissue, inflammation, chronic, focal | | 2 (4%) | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Callus | 1 (2%) | | | |
| Skeletal muscle | (1) | | (3) | (1) |
| Artery, inflammation, chronic | 1 (100%) | | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Atrophy, focal | | 1 (2%) | | |
| Meninges, hyperplasia, lymphoid | | | 1 (2%) | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | | | 1 (2%) |
| Hemorrhage | 1 (2%) | 5 (10%) | 2 (4%) | 5 (10%) |
| Hyperplasia, histiocytic | | | 2 (4%) | |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Infiltration cellular, mixed cell | | 1 (2%) | | |
| Thrombosis, chronic | 1 (2%) | | | |
| Alveolar epithelium, bronchiolization | | 33 (66%) | 41 (82%) | 49 (98%) |
| Alveolar epithelium, hyperplasia | 2 (4%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |
| Hemorrhage | | | 1 (2%) | |
| Inflammation, suppurative | 1 (2%) | 1 (2%) | | |
| Nasolacrimal duct, inflammation | | | | 1 (2%) |
| Squamous epithelium, nasolacrimal duct, hyperplasia, focal | | | | 1 (2%) |
| **Special Senses System** | | | | |
| None | | | | |

**TABLE D4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Urinary System** | | | | |
| Kidney | (49) | (50) | (50) | (50) |
| Congestion | | | 1 (2%) | |
| Hyperplasia, lymphoid | 1 (2%) | | 2 (4%) | |
| Infiltration cellular, mixed cell | 1 (2%) | | | |
| Metaplasia, focal, osseous | 1 (2%) | 1 (2%) | 1 (2%) | |
| Nephropathy | 11 (22%) | 7 (14%) | 9 (18%) | 3 (6%) |
| Renal tubule, accumulation, hyaline droplet | | 1 (2%) | 4 (8%) | |
| Renal tubule, casts protein | | | 1 (2%) | |
| Renal tubule, pigmentation | 1 (2%) | | | |
| Urinary bladder | (49) | (50) | (50) | (50) |
| Hyperplasia, lymphoid | | | 1 (2%) | |

# APPENDIX E
# GENETIC TOXICOLOGY

# GENETIC TOXICOLOGY

## *SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). *p*-Nitrotoluene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of *p*-nitrotoluene. The high dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

## MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by Myhr *et al.* (1985). *p*-Nitrotoluene was supplied as a coded aliquot by Radian Corporation. The high dose of 500 µg/mL was determined by solubility and toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained $6 \times 10^6$ cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with *p*-nitrotoluene continued for 4 hours, at which time the medium plus *p*-nitrotoluene was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% $CO_2$ for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male F344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for *p*-nitrotoluene to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a call of "questionable," and the absence of both a trend and peak response resulted in a "negative" call.

## CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). *p*-Nitrotoluene was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least two doses of *p*-nitrotoluene; the high dose was limited by solubility and toxicity. A single flask per dose was used, and all tests were repeated.

***Sister Chromatid Exchange Test:*** In the SCE test without S9, CHO cells were incubated for 25.5 hours with *p*-nitrotoluene in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 hours, the medium containing *p*-nitrotoluene was removed and replaced with fresh medium plus 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*-nitrotoluene, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *p*-nitrotoluene. Incubation proceeded for an additional 25.5 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Up to fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in some of the cultures, incubation time for those cultures was lengthened 7.3 to 10.3 hours to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

***Chromosomal Aberrations Test:*** In the Abs test without S9, cells were incubated in McCoy's 5A medium with *p*-nitrotoluene for 18 or 19 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *p*-nitrotoluene and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 18.3 or 19 hours in fresh medium, with Colcemid present for the final 2 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 periods were extended to allow accumulation of sufficient cells at harvest time.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype ($21 \pm 2$ chromosomes). All slides were scored blind, and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

## Rat and Mouse Bone Marrow Micronucleus Test Protocol

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by *p*-nitrotoluene exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male F344/N rats and $B6C3F_1$ mice were injected intraperitoneally (three times at 24-hour intervals) with *p*-nitrotoluene dissolved in corn oil. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored in up to five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dosed group is less than or equal to 0.025 divided by the number of dosed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

## Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

## Results

*p*-Nitrotoluene (3.3 to 1,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without Aroclor-induced rat or hamster liver S9 (Table E1, Haworth *et al.*, 1983). A positive response was observed with *p*-nitrotoluene in the L5178Y mouse lymphoma cell assay in trials conducted with Aroclor 1254-induced male Fisher rat liver S9 (Table E2). In the mouse lymphoma assay with S9, test chemical precipitation was observed in all four trials. Using acetone as the solvent in the first three trials conducted with S9, a precipitate formed at concentrations of 300 µg/mL and greater. In the fourth trial, the solvent was changed to ethanol in an effort to reduce precipitation. However, precipitation again occurred in the fourth trial. Because significant increases in mutant fraction were noted at doses that did not produce test chemical precipitation, the test was judged to be positive in the presence of S9. Significantly increased numbers of SCEs were induced by *p*-nitrotoluene in cultured CHO cells with and without S9 at doses that induced severe cell cycle delay, which is an indication of cytotoxicity (Table E3, Galloway *et al.*, 1987). Due to the observed levels of cytotoxicity, it should

be noted that indirect mechanisms such as increased BrdU incorporation or decreased DNA synthesis might have been involved in the increased levels of SCEs observed in these cells. *p*-Nitrotoluene also induced Abs in cultured CHO cells at the highest dose tested in each of two trials conducted with S9 (Table E4; Galloway *et al.*, 1987). As in the SCE test, the cytotoxicity of *p*-nitrotoluene, as evidenced by cell cycle delay, may be a factor in the interpretation of the positive Abs response; however, cytotoxicity was also evident in the absence of S9, and no increase in Abs was observed under those conditions (Table E4). *p*-Nitrotoluene caused no increases in micronucleated PCEs in the bone marrow of male rats (Table E5). In male mice, the results of the initial trial were considered positive, based on the responses seen at the two lowest doses; the trend test was not significant due to a downturn in the level of response at the highest dose of 600 mg/kg (Table E6). A second trial in mice failed to induce a significant increase in micronucleated PCEs over the same dose range, and the results of the test were therefore concluded to be negative overall.

**TABLE E1**
**Mutagenicity of *p*-Nitrotoluene 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** | 0.0 | 154 ± 10.8 | 127 ± 13.3 | 125 ± 4.4 | 145 ± 8.7 | 134 ± 6.3 | 128 ± 15.3 |
| | 3.3 | | 125 ± 10.5 | | | | |
| | 10.0 | 164 ± 8.7 | 141 ± 5.3 | | 131 ± 3.8 | | 118 ± 9.5 |
| | 33.0 | 155 ± 9.6 | 109 ± 6.5 | 131 ± 7.8 | 134 ± 6.9 | 145 ± 10.8 | 131 ± 3.9 |
| | 100.0 | 169 ± 0.9 | 124 ± 9.8 | 129 ± 4.5 | 136 ± 5.7 | 134 ± 10.1 | 137 ± 6.2 |
| | 333.0 | 177 ± 7.1[c] | 147 ± 3.8[c] | 141 ± 12.5 | 164 ± 5.5 | 156 ± 9.4 | 137 ± 4.5 |
| | 500.0 | | | | 143 ± 11.9[c] | | 136 ± 5.0[c] |
| | 667.0 | Toxic | | 155 ± 3.5[c] | | Toxic | |
| | 1,000.0 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control[d] | | 2,263 ± 120.4 | 1,343 ± 30.9 | 1,391 ± 136.2 | 1,191 ± 27.7 | 813 ± 60.8 | 1,061 ± 52.5 |
| **TA1535** | 0.0 | 30 ± 2.1 | 22 ± 2.0 | 12 ± 2.0 | 11 ± 2.1 | 14 ± 0.6 | 9 ± 0.3 |
| | 3.3 | | 24 ± 0.9 | | | | |
| | 10.0 | 39 ± 3.3 | 20 ± 1.3 | | 15 ± 0.7 | | 9 ± 1.9 |
| | 33.0 | 30 ± 1.9 | 19 ± 1.2 | 9 ± 0.9 | 10 ± 1.0 | 12 ± 0.3 | 14 ± 2.5 |
| | 100.0 | 35 ± 2.3 | 19 ± 3.0 | 19 ± 2.2 | 12 ± 2.2 | 13 ± 0.9 | 11 ± 1.7 |
| | 333.0 | 24 ± 0.9[c] | 21 ± 2.7[c] | 14 ± 2.9 | 17 ± 1.9 | 18 ± 3.5 | 16 ± 1.5 |
| | 500.0 | | | | 11 ± 2.6[c] | | 10 ± 1.5[c] |
| | 667.0 | Toxic | | Toxic | | Toxic | |
| | 1,000.0 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 1,469 ± 33.8 | 980 ± 33.6 | 121 ± 14.2 | 49 ± 2.5 | 56 ± 2.7 | 42 ± 3.5 |
| **TA1537** | 0.0 | 6 ± 1.5 | 5 ± 1.9 | 6 ± 0.3 | 4 ± 1.5 | 11 ± 1.5 | 7 ± 1.7 |
| | 3.3 | | 4 ± 2.6 | | | | |
| | 10.0 | 7 ± 0.3 | 5 ± 0.9 | | 7 ± 0.7 | | 7 ± 1.9 |
| | 33.0 | 5 ± 0.9 | 4 ± 1.5 | 6 ± 1.0 | 6 ± 0.3 | 13 ± 2.5 | 5 ± 2.0 |
| | 100.0 | 8 ± 1.5 | 3 ± 1.2 | 10 ± 2.2 | 7 ± 0.0 | 10 ± 2.4 | 6 ± 1.0 |
| | 333.0 | 7 ± 2.7[c] | 4 ± 0.7 | 7 ± 0.9 | 5 ± 2.5 | 12 ± 3.5 | 6 ± 2.7 |
| | 500.0 | | | | 6 ± 1.0[c] | | 6 ± 1.0[c] |
| | 667.0 | Toxic | | Toxic | | Toxic | |
| | 1,000.0 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 557 ± 68.4 | 379 ± 61.2 | 130 ± 11.5 | 133 ± 3.8 | 46 ± 7.1 | 77 ± 6.1 |
| **TA98** | 0.0 | 25 ± 2.7 | 13 ± 1.7 | 30 ± 3.6 | 23 ± 2.1 | 31 ± 2.3 | 23 ± 5.6 |
| | 3.3 | | 11 ± 0.6 | | | | |
| | 10.0 | 16 ± 2.4 | 15 ± 1.7 | | 23 ± 2.5 | | 23 ± 2.3 |
| | 33.0 | 19 ± 4.0 | 15 ± 1.2 | 36 ± 3.3 | 22 ± 0.3 | 35 ± 3.4 | 20 ± 1.2 |
| | 100.0 | 18 ± 1.9 | 14 ± 1.3 | 31 ± 2.3 | 27 ± 4.5 | 31 ± 2.0 | 24 ± 4.1 |
| | 333.0 | 20 ± 1.9[c] | 11 ± 2.0 | 36 ± 4.2 | 27 ± 1.2 | 27 ± 2.8 | 22 ± 0.9 |
| | 500.0 | | | | 21 ± 5.0[c] | | 16 ± 2.0[c] |
| | 667.0 | Toxic | | Toxic | | 17 ± 0.6[c] | |
| | 1,000.0 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 904 ± 87.8 | 1,347 ± 43.7 | 1,468 ± 63.0 | 1,045 ± 12.6 | 515 ± 10.9 | 752 ± 10.7 |

[a] Study was performed at EG&G Mason Research Institute. The detailed protocol and these data are presented by Haworth *et al.* (1983).
[b] 0 µg/plate was the solvent control. Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene[a]**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction[b] | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **-S9** | | | | | | |
| **Trial 1** | | | | | | |
| Ethanol[c] | | 68 | 89 | 60 | 29 | |
| | | 90 | 104 | 92 | 34 | |
| | | 100 | 108 | 89 | 30 | 31 |
| *p*-Nitrotoluene | 75 | 56 | 61 | 45 | 27 | |
| | | 90 | 66 | 73 | 27 | |
| | | 84 | 79 | 50 | 20 | 25 |
| | 100 | 81 | 72 | 53 | 22 | |
| | | 58 | 51 | 51 | 30 | |
| | | 61 | 44 | 50 | 27 | 26 |
| | 150 | 67 | 52 | 68 | 34 | |
| | | 81 | 81 | 69 | 28 | 31 |
| | 180 | 85 | 48 | 70 | 27 | |
| | | 72 | 38 | 82 | 38 | |
| | | 86 | 41 | 124 | 48 | 38 |
| | 200 | 59 | 29 | 81 | 46 | |
| | | 52 | 22 | 79 | 50 | |
| | | 58 | 32 | 53 | 30 | 42 |
| | 240 | 30 | 14 | 42 | 47 | |
| | | 46 | 21 | 77 | 56 | |
| | | 51 | 19 | 68 | 45 | 49* |
| Methylmethanesulfonate[d] | 5 | 37 | 24 | 534 | 483 | |
| | | 47 | 28 | 511 | 361 | |
| | | 47 | 30 | 492 | 349 | 398* |

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **-S9** (continued) | | | | | | |
| **Trial 2** | | | | | | |
| Ethanol | | 81 | 77 | 44 | 18 | |
| | | 83 | 102 | 48 | 19 | |
| | | 103 | 121 | 54 | 17 | 18 |
| *p*-Nitrotoluene | 25 | 109 | 81 | 73 | 22 | |
| | | 113 | 82 | 71 | 21 | |
| | | 109 | 87 | 58 | 18 | 20 |
| | 50 | 116 | 72 | 77 | 22 | |
| | 75 | 104 | 56 | 49 | 16 | |
| | | 109 | 73 | 45 | 14 | 15 |
| | 100 | 114 | 50 | 58 | 17 | |
| | | 103 | 56 | 60 | 19 | |
| | | 59 | 38 | 70 | 40 | 25 |
| | 150 | 95 | 43 | 79 | 28 | |
| | | 76 | 39 | 79 | 35 | |
| | | 94 | 38 | 67 | 24 | 29* |
| | 250 | 36 | 11 | 50 | 47 | |
| | | 60 | 13 | 66 | 37 | |
| | | 80 | 24 | 53 | 22 | 35* |
| Methylmethanesulfonate | 5 | 96 | 55 | 345 | 120 | |
| | | 68 | 42 | 405 | 198 | 159* |

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **+S9** | | | | | | |
| **Trial 1** | | | | | | |
| Acetone[c] | | 105 | 101 | 77 | 24 | |
| | | 88 | 81 | 70 | 26 | |
| | | 97 | 105 | 52 | 18 | |
| | | 105 | 114 | 59 | 19 | 22 |
| *p*-Nitrotoluene | 50 | 87 | 76 | 96 | 37 | |
| | | 83 | 93 | 63 | 25 | |
| | | 84 | 77 | 105 | 42 | 35* |
| | 75 | 82 | 68 | 100 | 41 | |
| | | 68 | 63 | 77 | 38 | |
| | | 94 | 74 | 78 | 28 | 35* |
| | 100 | 102 | 71 | 130 | 42 | |
| | | 87 | 57 | 120 | 46 | |
| | | 86 | 61 | 87 | 34 | 41* |
| | 150 | 77 | 60 | 111 | 48 | |
| | | 80 | 63 | 85 | 35 | |
| | | 68 | 57 | 85 | 42 | 42* |
| | 200 | 103 | 42 | 170 | 55 | |
| | | 97 | 53 | 109 | 38 | |
| | | 80 | 40 | 129 | 54 | 49* |
| | 300[e] | 108 | 41 | 141 | 44 | |
| | | 91 | 43 | 71 | 26 | 35 |
| | 500 | Toxic | | | | |
| | | Toxic | | | | |
| Methylcholanthrene[d] | 2.5 | 81 | 50 | 337 | 140 | |
| | | 91 | 48 | 328 | 120 | |
| | | 75 | 42 | 319 | 143 | 134* |

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **+S9** (continued) | | | | | | |
| **Trial 2** | | | | | | |
| Acetone | | 91 | 107 | 69 | 25 | |
| | | 90 | 84 | 66 | 24 | |
| | | 104 | 115 | 71 | 23 | |
| | | 94 | 94 | 72 | 26 | 25 |
| *p*-Nitrotoluene | 50 | 101 | 81 | 86 | 28 | |
| | | 72 | 102 | 61 | 28 | |
| | | 86 | 83 | 64 | 25 | 27 |
| | 75 | 72 | 77 | 60 | 28 | |
| | | 105 | 88 | 65 | 21 | |
| | | 104 | 80 | 68 | 22 | 23 |
| | 100 | 108 | 86 | 82 | 25 | |
| | | 117 | 79 | 91 | 26 | |
| | | 109 | 89 | 113 | 35 | 29 |
| | 150 | 111 | 69 | 113 | 34 | |
| | | 108 | 98 | 112 | 34 | |
| | | 104 | 78 | 87 | 28 | 32 |
| | 200 | 90 | 72 | 89 | 33 | |
| | | 109 | 71 | 120 | 37 | |
| | | 112 | 67 | 123 | 36 | 35 |
| | 300[e] | 99 | 47 | 149 | 50 | |
| | | 106 | 57 | 122 | 38 | |
| | | 110 | 45 | 106 | 32 | 40* |
| | 500 | Toxic | | | | |
| | | Toxic | | | | |
| Methylcholanthrene | 2.5 | 56 | 51 | 484 | 286 | |
| | | 98 | 109 | 363 | 124 | |
| | | 85 | 68 | 501 | 198 | 203* |

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **+S9** (continued) | | | | | | |
| **Trial 3** | | | | | | |
| Acetone | | 79 | 115 | 85 | 36 | |
| | | 102 | 108 | 139 | 45 | |
| | | 104 | 90 | 128 | 41 | |
| | | 101 | 87 | 122 | 40 | 41 |
| *p*-Nitrotoluene | 50 | 107 | 70 | 219 | 69 | |
| | | 110 | 68 | 185 | 56 | |
| | | 120 | 65 | 178 | 49 | 58 |
| | 75 | 84 | 61 | 181 | 72 | |
| | | 103 | 69 | 263 | 85 | |
| | | 112 | 48 | 175 | 52 | 70* |
| | 100 | 113 | 62 | 263 | 78 | |
| | | 111 | 44 | 234 | 70 | |
| | | 86 | 37 | 162 | 63 | 70* |
| | 150 | 93 | 35 | 251 | 90 | |
| | | 105 | 39 | 380 | 120 | |
| | | 87 | 31 | 205 | 79 | 96* |
| | 200 | 86 | 17 | 436 | 170 | |
| | | 90 | 22 | 353 | 131 | 150* |
| | 300[e] | 75 | 8 | 418 | 186 | |
| | | 84 | 13 | 472 | 187 | |
| | | 38 | 4 | 479 | 424 | 266* |
| | 500 | Toxic | | | | |
| | | Toxic | | | | |
| | | Toxic | | | | |
| Methylcholanthrene | 2.5 | 51 | 21 | 842 | 549 | |
| | | 55 | 21 | 1,031 | 623 | |
| | | 67 | 34 | 995 | 497 | 556* |

**TABLE E2**
**Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by *p*-Nitrotoluene**

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---|---|---|---|---|---|---|
| **+S9** (continued) | | | | | | |
| **Trial 4** | | | | | | |
| Ethanol | | 88 | 91 | 108 | 41 | |
| | | 106 | 101 | 93 | 29 | |
| | | 118 | 108 | 118 | 33 | 34 |
| *p*-Nitrotoluene | 50 | 77 | 52 | 160 | 70 | |
| | | 109 | 82 | 144 | 44 | |
| | | 108 | 61 | 139 | 43 | 52* |
| | 100 | 108 | 59 | 204 | 63 | |
| | | 97 | 52 | 180 | 62 | 62* |
| | 150 | 97 | 45 | 189 | 65 | |
| | | 111 | 50 | 124 | 37 | 51 |
| | 200 | 98 | 40 | 205 | 70 | |
| | | 118 | 39 | 233 | 66 | |
| | | 88 | 31 | 316 | 119 | 85* |
| | 250[e] | 103 | 28 | 194 | 63 | |
| | | 94 | 29 | 300 | 107 | |
| | | 105 | 32 | 249 | 79 | 83* |
| | 300[e] | 92 | 19 | 272 | 98 | |
| | | 83 | 13 | 388 | 156 | |
| | | 94 | 29 | 192 | 68 | 108* |
| Methylcholanthrene | 2.5 | 96 | 65 | 785 | 272 | |
| | | 92 | 41 | 952 | 346 | |
| | | 91 | 43 | 726 | 266 | 294* |

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented by Myhr *et al.* (1985).
[b] Mutant fraction=mutant cells/$10^6$ clonable cells
[c] Solvent control
[d] Positive control
[e] Precipitate of *p*-nitrotoluene formed at this concentration.

**TABLE E3**
**Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrotoluene[a]**

| Compound | Dose (µg/mL) | Total Cells Scored | No. of Chromo-somes | No. of SCEs | SCEs/ Chromo-some | SCEs/ Cell | Hrs in BrdU | Relative Change of SCEs/ Chromosome[b] (%) |
|---|---|---|---|---|---|---|---|---|
| **-S9** | | | | | | | | |
| **Trial 1** | | | | | | | | |
| Summary: Weakly positive | | | | | | | | |
| Dimethylsulfoxide[c] | | 50 | 1,038 | 487 | 0.46 | 9.7 | 25.5 | |
| *p*-Nitrotoluene | 50 | 43 | 889 | 382 | 0.42 | 8.9 | 25.5 | -8.42 |
| | 167 | 50 | 1,024 | 576 | 0.56 | 11.5 | 32.8[e] | 19.89 |
| | 500[d] | 50 | 1,018 | 637 | 0.62 | 12.7 | 32.8[e] | 33.37* |
| | | | | | P<0.001[f] | | | |
| Mitomycin-C[g] | 0.005 | 25 | 520 | 798 | 1.53 | 31.9 | 25.5 | 227.09* |
| **Trial 2** | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,036 | 532 | 0.51 | 10.6 | 25.5 | |
| *p*-Nitrotoluene | 200[d] | 50 | 1,035 | 732 | 0.70 | 14.6 | 35.8[e] | 37.73* |
| | 300[d] | 50 | 1,032 | 698 | 0.67 | 14.0 | 35.8[e] | 31.71* |
| | 400[d] | 50 | 1,034 | 803 | 0.77 | 16.1 | 35.8[e] | 51.23* |
| | 500[d] | Toxic | | | | | 35.8[e] | |
| | | | | | P<0.001 | | | |
| Mitomycin-C | 0.005 | 25 | 522 | 596 | 1.14 | 23.8 | 25.5 | 122.34* |

**TABLE E3**
**Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrotoluene**

| Compound | Dose (µg/mL) | Total Cells Scored | No. of Chromo-somes | No. of SCEs | SCEs/ Chromo-some | SCEs/ Cell | Hrs in BrdU | Relative Change of SCEs/ Chromosome (%) |
|---|---|---|---|---|---|---|---|---|
| **+S9** | | | | | | | | |
| **Trial 1** | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,042 | 467 | 0.44 | 9.3 | 25.5 | |
| *p*-Nitrotoluene | 50 | 50 | 1,043 | 464 | 0.44 | 9.3 | 25.5 | -0.74 |
| | 167 | 50 | 1,044 | 480 | 0.45 | 9.6 | 25.5 | 2.59 |
| | 500[d] | 50 | 1,031 | 510 | 0.49 | 10.2 | 25.5 | 10.37 |
| | | | | | P=0.052 | | | |
| Cyclophosphamide[g] | 1.5 | 25 | 525 | 1,082 | 2.06 | 43.3 | 25.5 | 359.86* |
| **Trial 2** | | | | | | | | |
| Summary: Weakly positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,041 | 467 | 0.44 | 9.3 | 25.5 | |
| *p*-Nitrotoluene | 600[d] | 50 | 1,027 | 535 | 0.52 | 10.7 | 25.5 | 16.12 |
| | 700[d] | 50 | 1,030 | 657 | 0.63 | 13.1 | 35.5[e] | 42.19* |
| | | | | | P<0.001 | | | |
| Cyclophosphamide | 1.5 | 25 | 517 | 654 | 1.26 | 26.2 | 25.5 | 181.99* |
| **Trial 3** | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,047 | 451 | 0.43 | 9.0 | 25.5 | |
| *p*-Nitrotoluene | 550[d] | 50 | 1,038 | 905 | 0.87 | 18.1 | 25.5 | 102.41* |
| | 600[d] | 50 | 1,032 | 787 | 0.76 | 15.7 | 25.5 | 77.04* |
| | 650[d] | 50 | 1,039 | 886 | 0.85 | 17.7 | 25.5 | 97.97* |
| | | | | | P<0.001 | | | |
| Cyclophosphamide | 1.5 | 25 | 521 | 872 | 1.67 | 34.9 | 25.5 | 288.55* |

* Positive (≥20% increase over solvent control)
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Precipitate formed at this dose.
[e] Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[f] Significance of relative SCEs/chromosome tested by the linear regression trend test versus log of the dose
[g] Positive control

**TABLE E4**
**Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *p*-Nitrotoluene[a]**

| Compound | Dose (µg/mL) | Total Cells Scored | Number of Aberrations | Aberrations/ Cell | Cells with Aberrations (%) |
|---|---|---|---|---|---|
| **-S9** | | | | | |
| **Trial 1** | | | | | |
| Harvest time: 20.0 hours[b] | | | | | |
| Summary: Negative | | | | | |
| Dimethylsulfoxide[c] | | 100 | 3 | 0.03 | 3.0 |
| *p*-Nitrotoluene | 300 | 100 | 7 | 0.07 | 7.0 |
| | 400 | 100 | 10 | 0.1 | 10.0 |
| | 500 | 100 | 9 | 0.09 | 9.0 |
| | | | | | P=0.032[d] |
| Mitomycin-C[e] | 0.062 | 50 | 24 | 0.48 | 32.0 |
| **Trial 2** | | | | | |
| Harvest time: 21.0 hours[b] | | | | | |
| Summary: Negative | | | | | |
| Dimethylsulfoxide | | 100 | 7 | 0.07 | 7.0 |
| *p*-Nitrotoluene | 300 | 100 | 9 | 0.09 | 8.0 |
| | 400 | 100 | 0 | 0 | 0.0 |
| | 500 | 100 | 6 | 0.06 | 5.0 |
| | | | | | P=0.897 |
| Mitomycin-C | 0.062 | 50 | 30 | 0.6 | 44.0 |

**TABLE E4**
**Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *p*-Nitrotoluene**

| Compound | Dose (µg/mL) | Total Cells Scored | Number of Aberrations | Aberrations/ Cell | Cells with Aberrations (%) |
|---|---|---|---|---|---|
| **+S9** | | | | | |
| **Trial 1** | | | | | |
| Harvest time: 20.3 hours[b] | | | | | |
| Summary: Weakly positive | | | | | |
| Dimethylsulfoxide | | 100 | 9 | 0.09 | 8.0 |
| *p*-Nitrotoluene | 500[f] | 100 | 12 | 0.12 | 7.0 |
| | 550[f] | 100 | 10 | 0.1 | 8.0 |
| | 600[f] | 100 | 30 | 0.3 | 24.0* |
| | | | | | P<0.001 |
| Cyclophosphamide[e] | 10 | 50 | 40 | 0.8 | 44.0* |
| **Trial 2** | | | | | |
| Harvest time: 21.0 hours[b] | | | | | |
| Summary: Weakly positive | | | | | |
| Dimethylsulfoxide | | 100 | 7 | 0.07 | 7.0 |
| *p*-Nitrotoluene | 400 | 100 | 3 | 0.03 | 3.0 |
| | 500 | 100 | 2 | 0.02 | 2.0 |
| | 550 | 100 | 23 | 0.23 | 21.0* |
| | | | | | P=0.003 |
| Cyclophosphamide | 10 | 50 | 14 | 0.28 | 26.0* |

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987).
[b] Due to *p*-nitrotoluene-induced cell cycle delay, harvest time was extended to maximize the number of first-division metaphase cells available for analysis.
[c] Solvent control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[e] Positive control
[f] Precipitate formed at this dose.

**TABLE E5**
**Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with *p*-Nitrotoluene by Intraperitoneal Injection[a]**

| Compound | Dose (mg/kg) | Number of Rats with Erythrocytes Scored | Micronucleated PCEs/ 1,000 PCEs[b] | P Value[c] |
|---|---|---|---|---|
| Corn oil[d] | 0 | 5 | 0.80 ± 0.12 | |
| *p*-Nitrotoluene | 150 | 5 | 1.00 ± 0.22 | 0.3186 |
| | 300 | 5 | 0.80 ± 0.12 | 0.5000 |
| | 600 | 5 | 0.90 ± 0.33 | 0.4041 |
| | | | P=0.466[e] | |
| Cyclophosphamide[f] | 25 | 5 | 10.30 ± 2.79 | 0.0000 |

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al.* (1993).
[b] PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.008; positive control values are significant at P≤0.05 (ILS, 1990).
[e] Vehicle control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
Positive control

**TABLE E6**
**Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with *p*-Nitrotoluene by Intraperitoneal Injection[a]**

| Compound | Dose (mg/kg) | Number of Mice with Erythrocytes Scored | Micronucleated PCEs/ 1,000 PCEs[b] | P Value[c] |
|---|---|---|---|---|
| **Trial 1** | | | | |
| Corn oil[d] | 0 | 5 | 0.90 ± 0.10 | |
| *p*-Nitrotoluene | 150 | 5 | 2.20 ± 0.37 | 0.0097 |
| | 300 | 5 | 2.50 ± 0.35 | 0.0030 |
| | 600 | 5 | 1.70 ± 0.37 | 0.0582 |
| | | | P=0.166[e] | |
| Cyclophosphamide[f] | 25 | 5 | 6.20 ± 1.15 | 0.0000 |
| **Trial 2** | | | | |
| Corn oil | 0 | 5 | 1.50 ± 0.32 | |
| *p*-Nitrotoluene | 150 | 5 | 1.90 ± 0.33 | 0.2462 |
| | 300 | 5 | 1.60 ± 0.29 | 0.4287 |
| | 600 | 5 | 2.20 ± 0.37 | 0.1247 |
| | | | P=0.150 | |
| Cyclophosphamide | 25 | 3 | 4.67 ± 0.60 | 0.0001 |

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al.* (1993).
[b] PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.008; positive control values are significant at P≤0.05 (ILS, 1990)
[e] Vehicle control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
Positive control

# APPENDIX F
# *p*-ACETAMIDOBENZOIC ACID AND *p*-NITROBENZOIC ACID — BIOMARKERS OF EXPOSURE

# *p*-ACETAMIDOBENZOIC ACID AND *p*-NITROBENZOIC ACID — BIOMARKERS OF EXPOSURE

## INTRODUCTION

The biotransformation studies of *p*-nitrotoluene in rats indicate three major metabolic pathways: oxidation of the methyl group, reduction of the nitro group, and hydroxylation of the ring (Chism *et al.*, 1984). To understand how the relative contribution of these pathways may change with chronic exposure and age and to establish the correlation between exposure concentration and internal dose, two urinary metabolites were followed during the 2-year studies of *p*-nitrotoluene, *p*-acetamidobenzoic acid and *p*-nitrobenzoic acid. Ring hydroxylation is a relatively minor pathway in rats.

## MATERIALS AND METHODS

Urinary metabolites were quantitated by high-performance liquid chromatography using a C-18 column. A mobile phase of A) 0.01 M potassium phosphate buffer:methanol (85:15) and B) 0.01 M potassium phosphate buffer:methanol (50:50) was used; the pH of each mixture was adjusted to 2.6 to 2.7 with phosphoric acid. The flow rate was 1 mL per minute, and it was programmed to deliver 100% A for 1 minute, then linearly increase to 20% A:80% B over 20 minutes. Detection was by ultraviolet absorption (266 nm). The limits of quantitation were 0.227 mg/mL for *p*-nitrobenzoic acid and 0.0112 mg/mL for *p*-acetamidobenzoic acid.

## RESULTS AND DISCUSSION

Comparisons among the metabolite data were made on the metabolite to creatinine ratio obtained by dividing the metabolite concentration by creatinine concentration. Creatinine excretion is considered to be related to muscle mass. Thus, normalizing the metabolite data to creatinine in effect normalizes the metabolite to body weight. It was considered necessary to do this as comparisons are being made across time as the animals' weights change and between sexes, males are generally heavier than females. The efficiency of urine collection in a metabolism cage is not 100%, so calculation of total metabolite based on the amount of urine collected has some uncertainty. Basing the comparison on concentrations of creatinine and metabolite in measured aliquots eliminates the need to know the total urine output and the associated uncertainties.

The ratios of *p*-acetamidobenzoic acid to creatinine excreted in urine by rats are shown in Table F1. The ratios for male and female rats were larger at 2 weeks compared to later time points. Generally, the ratios were larger for females than males. The *p*-acetamidobenzoic acid/creatinine ratios were related linearly with exposure concentration.

The ratios of *p*-nitrobenzoic acid to creatinine excreted in urine by rats are also shown in Table F1. The *p*-nitrobenzoic acid/creatinine ratios were higher at 2 weeks than at later time points for both males and females. In contrast to the acetamidobenzoic acid/creatinine ratios, there are no significant differences between sexes. The *p*-nitrobenzoic acid/creatinine ratios were linearly related to concentration.

Urinary excretion of *p*-nitrobenzoic acid and *p*-acetamidobenzoic acid by mice is shown in Table F2. The concentrations of the metabolites appeared to increase with exposure concentration, but too many data are missing for detailed comparisons. In some cases there was insufficient urine for analysis, or the metabolite concentration was below the limit of quantitation.

**TABLE F1**
**Urinary Biomarker Data for Rats in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| n | 5 | 5 | 5 | 5 |
| **Male** | | | | |
| Volume (mL/24 hours) | | | | |
| Week 2 | 4.0 ± 0.5 | 4.4 ± 0.5 | 4.4 ± 0.8 | 4.0 ± 0.7 |
| Month 3 | 3.8 ± 0.6 | 5.0 ± 0.3 | 4.7 ± 1.4 | 5.2 ± 1.1 |
| Month 12 | 3.9 ± 0.6 | 4.2 ± 0.3 | 4.9 ± 1.3 | 7.3 ± 0.6 |
| Month 18 | 5.5 ± 0.7 | 7.1 ± 0.7 | 6.8 ± 0.7 | 7.9 ± 0.9 |
| Creatinine (mg/dL) | | | | |
| Week 2 | 182 ± 15 | 138 ± 11 | 124 ± 11 | 93 ± 7 |
| Month 3 | 216 ± 20 | 165 ± 11 | 175 ± 14 | 147 ± 8 |
| Month 12 | 304 ± 29 | 251 ± 10 | 180 ± 12 | 167 ± 10 |
| Month 18 | 230 ± 25 | 186 ± 15 | 182 ± 10 | 147 ± 4 |
| *p*-Acetamidobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0.0036 ± 0.0072 | 1.54 ± 0.59 | 3.30 ± 1.62 | 7.51 ± 2.09 |
| Month 3 | 0 ± 0 | 0.692 ± 0.111 | 1.42 ± 0.92 | 8.58 ± 4.05 |
| Month 12 | 0.0356 ± 0.0260 | 0.514 ± 0.108 | 1.08 ± 0.73 | 5.96 ± 1.42 |
| Month 18 | 0 ± 0 | 0.893 ± 0.344 | 1.61 ± 0.44 | 7.24 ± 2.40 |
| *p*-Acetamidobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0.000645 ± 0.00129 | 0.247 ± 0.053 | 0.601 ± 0.176▲ | 2.12 ± 0.18 |
| Month 3 | 0 ± 0 | 0.0848 ± 0.0071*▲ | 0.176 ± 0.036*▲ | 1.16 ± 0.29* |
| Month 12 | 0.00327 ± 0.00197 | 0.0487 ± 0.0056*▲ | 0.112 ± 0.026*▲ | 0.491 ± 0.089*▲ |
| Month 18 | 0 ± 0 | 0.0786 ± 0.0540*▲ | 0.131 ± 0.0209*▲ | 0.614 ± 0.102*▲ |
| *p*-Nitrobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0 ± 0 | 13.4 ± 5.4 | 26.5 ± 12.3 | 30.9 ± 15.5 |
| Month 3 | 0 ± 0 | 8.30 ± 1.72 | 15.5 ± 10.6 | 20.1 ± 9.6 |
| Month 12 | 0 ± 0 | 8.49 ± 1.76 | 15.8 ± 11.3 | 37.5 ± 8.3 |
| Month 18 | 0 ± 0 | 11.2 ± 2.8 | 22.5 ± 5.9 | 28.2 ± 7.3 |
| *p*-Nitrobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0 ± 0 | 2.14 ± 0.31 | 4.90 ± 1.66 | 8.29 ± 2.71 |
| Month 3 | 0 ± 0 | 1.01 ± 0.11* | 1.80 ± 0.38* | 2.55 ± 0.92* |
| Month 12 | 0 ± 0 | 0.805 ± 0.083* | 1.59 ± 0.44* | 3.11 ± 0.58* |
| Month 18 | 0 ± 0 | 0.866 ± 0.130* | 1.83 ± 0.30* | 2.47 ± 0.41* |

**TABLE F1**
**Urinary Biomarker Data for Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| n | 5 | 5 | 5 | 5 |
| **Female** | | | | |
| Volume (mL/24 hours) | | | | |
| Week 2 | 3.6 ± 1.0 | 3.6 ± 0.7 | 5.4 ± 0.9 | 4.6 ± 0.9 |
| Month 3 | 2.4 ± 0.8 | 4.2 ± 0.7 | 5.6 ± 1.1 | 4.6 ± 0.7 |
| Month 12 | 6.5 ± 0.9 | 4.1 ± 0.7 | 6.7 ± 0.9 | 5.6 ± 0.9 |
| Month 18 | 8.7 ± 2.1 | 11.9 ± 1.8 | 10.6 ± 1.9 | 5.8 ± 1.6 |
| Creatinine (mg/dL) | | | | |
| Week 2 | 130 ± 20 | 112 ± 7 | 83 ± 8 | 90 ± 13 |
| Month 3 | 130 ± 9 | 129 ± 23 | 108 ± 11 | 107 ± 10 |
| Month 12 | 127 ± 11 | 156 ± 21 | 116 ± 19 | 120 ± 14 |
| Month 18 | 121 ± 21 | 87 ± 7 | 91 ± 8 | 91 ± 5 |
| *p*-Acetamidobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0 ± 0 | 0.989 ± 0.238 | 4.95 ± 0.97 | 8.06 ± 1.33 |
| Month 3 | 0 ± 0 | 0.788 ± 0.275 | 2.29 ± 0.79 | 6.39 ± 2.13 |
| Month 12 | 0.0344 ± 0.0298 | 0.612 ± 0.092 | 3.41 ± 1.48 | 5.77 ± 1.85 |
| Month 18 | 0 ± 0 | 1.15 ± 0.17 | 4.55 ± 1.90 | 7.95 ± 4.18 |
| *p*-Acetamidobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0 ± 0 | 0.241 ± 0.020 | 1.15 ± 0.17 | 2.10 ± 0.28 |
| Month 3 | 0 ± 0 | 0.164 ± 0.056 | 0.402 ± 0.071 | 1.34 ± 0.305* |
| Month 12 | 0.00442 ± 0.00376 | 0.107 ± 0.021* | 0.482 ± 0.212* | 0.895 ± 0.165* |
| Month 18 | 0 ± 0 | 0.116 ± 0.012* | 0.495 ± 0.154* | 1.55 ± 0.306 |
| *p*-Nitrobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0 ± 0 | 7.49 ± 1.81 | 24.7 ± 3.3 | 27.1 ± 4.6 |
| Month 3 | 0 ± 0 | 6.21 ± 1.81 | 13.0 ± 3.4 | 18.6 ± 2.3 |
| Month 12 | 0 ± 0 | 5.44 ± 2.22 | 13.1 ± 3.5 | 19.5 ± 8.8 |
| Month 18 | 0 ± 0 | 12.2 ± 2.2 | 19.1 ± 6.8 | 16.5 ± 8.8 |
| *p*-Nitrobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0 ± 0 | 1.86 ± 0.29 | 5.81 ± 0.54 | 7.15 ± 1.02 |
| Month 3 | 0 ± 0 | 1.29 ± 0.33 | 2.32 ± 0.50* | 4.03 ± 0.76* |
| Month 12 | 0 ± 0 | 0.927 ± 0.364* | 1.84 ± 0.46* | 2.93 ± 0.65* |
| Month 18 | 0 ± 0 | 1.23 ± 0.16 | 2.02 ± 0.21* | 3.12 ± 0.39* |

* Significantly different ($P \leq 0.01$) from 2-week data by Fisher's least significant difference test
▲ Significantly different ($P \leq 0.01$) from corresponding female data by Fisher's least significant difference test
[a] Data are presented as mean ± standard error.

**TABLE F2**
**Urinary Biomarker Data for Mice in the 2-Year Feed Study of *p*-Nitrotoluene[a]**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Male** | | | | |
| n | | | | |
| Week 2 | 1 | 4 | 2 | 4 |
| Month 3 | 2 | 2 | 2 | 3 |
| Month 12 | 5 | 5 | 5 | 5 |
| Month 18 | 5 | 5 | 5 | 5 |
| Volume (mL/24 hours) | | | | |
| Week 2 | 0.3 | 0.4 ± 0.1 | 0.5 ± 0.3 | 0.4 ± 0.2 |
| Month 3 | 0.2 ± 0.1 | 0.7 ± 0.3 | 0.6 ± 0.4 | 0.1 ± 0.0 |
| Month 12 | 1.5 ± 0.2 | 1.2 ± 0.1 | 1.4 ± 0.2 | 0.9 ± 0.0 |
| Month 18 | 0.7 ± 0.1 | 1.1 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.1 |
| Creatinine (mg/dL) | | | | |
| Week 2 | 66.0 | 54.4 ± 3.0 | 71.8 ± 3.8 | 39.9 ± 4.4 |
| Month 3 | 12.8 ± 11.8 | 36.3 ± 19.3 | 40.0 ± 22.5 | 2.17 ± 1.67 |
| Month 12 | 47.2 ± 4.8 | 43.6 ± 1.5 | 38.4 ± 2.8 | 47.7 ± 3.3 |
| Month 18 | 57.1 ± 5.1 | 53.5 ± 6.0 | 41.5 ± 3.6 | 42.9 ± 2.9 |
| *p*-Acetamidobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0.00783 | 0.0101 ± 0.0044 | 0.0430 ± 0.022 | 0.0746 ± 0.0884 |
| Month 3 | 0 ± 0 | 0.0114 ± 0.0077 | 0.0272 ± 0.0254 | 0.000643 ± 0.000910 |
| Month 12 | 0 ± 0 | 0.00280 ± 0.00560 | 0.0068 ± 0.0135 | 0.0451 ± 0.0148 |
| Month 18 | 0 ± 0 | 0.00897 ± 0.00561 | 0.0245 ± 0.0194 | 0.0504 ± 0.0125 |
| *p*-Acetamidobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0.0395 | 0.0479 ± 0.0139 | 0.138 ± 0.015 | 0.408 ± 0.215 |
| Month 3 | 0 ± 0 | 0.0445 ± 0.0099 | 0.0674 ± 0.0168 | 0.117 ± 0.165 |
| Month 12 | 0 ± 0 | 0.00609 ± 0.01217 | 0.0112 ± 0.0225 | 0.0986 ± 0.0191 |
| Month 18 | 0 ± 0 | 0.0186 ± 0.0110 | 0.0522 ± 0.0421 | 0.101 ± 0.0308 |
| *p*-Nitrobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0 | 0.0160 ± 0.0277 | 0.204 ± 0.110 | 0.304 ± 0.385 |
| Month 3 | 0 ± 0 | 0 ± 0 | 0.122 ± 0.122 | 0.00367 ± 0.00519 |
| Month 12 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.105 ± 0.092 |
| Month 18 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.109 ± 0.117 |
| *p*-Nitrobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0 | 0.0447 ± 0.0809 | 0.640 ± 0.047 | 1.58 ± 0.95 |
| Month 3 | 0 ± 0 | 0 ± 0 | 0.194 ± 0.194 | 0.667 ± 0.943 |
| Month 12 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.210 ± 0.182 |
| Month 18 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0.218 ± 0.215 |

**TABLE F2**
**Urinary Biomarker Data for Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | 1,250 ppm | 2,500 ppm | 5,000 ppm |
|---|---|---|---|---|
| **Female** | | | | |
| n | | | | |
| Week 2 | 2 | 1 | 3 | 3 |
| Month 3 | 5 | 4 | 5 | 5 |
| Month 12 | 5 | 5 | 5 | 5 |
| Month 18 | 5 | 5 | 5 | 5 |
| Volume (mL/24 hours) | | | | |
| Week 2 | 0.5 ± 0.4 | 0.3 | 0.2 ± 0.0 | 0.2 ± 0.1 |
| Month 3 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.3 ± 0.1 | 0.5 ± 0.2 |
| Month 12 | 1.0 ± 0.1 | 0.9 ± 0.2 | 0.8 ± 0.1 | 0.6 ± 0.1 |
| Month 18 | 0.7 ± 0.1 | 1.0 ± 0.3 | 1.1 ± 0.1 | 1.0 ± 0.1 |
| Creatinine (mg/dL) | | | | |
| Week 2 | 69.3 ± 11.8 | 89.0 | 64.7 ± 18.7 | 23.5 ± 1.8 |
| Month 3 | 46.4 ± 12.6 | 59.0 ± 10.7 | 28.5 ± 6.2 | 35.2 ± 8.3 |
| Month 12 | 42.3 ± 4.9 | 46.8 ± 4.7 | 49.9 ± 3.6 | 55.6 ± 6.0 |
| Month 18 | 68.0 ± 10.1 | 46.0 ± 3.9 | 46.0 ± 3.9 | 46.0 ± 2.1 |
| *p*-Acetamidobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0.000625 ± 0.000625 | 0.0280 | 0.0155 ± 0.0054 | 0.0456 ± 0.0175 |
| Month 3 | 0 ± 0 | 0.00821 ± 0.00397 | 0.0139 ± 0.0128 | 0.0731 ± 0.0807 |
| Month 12 | 0 ± 0 | 0.0059 ± 0.0117 | 0.00714 ± 0.00960 | 0.0972 ± 0.0674 |
| Month 18 | 0 ± 0 | 0.00411 ± 0.00545 | 0.0310 ± 0.0152 | 0.104 ± 0.036 |
| *p*-Acetamidobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0.0077 ± 0.0077 | 0.105 | 0.162 ± 0.042 | 1.32 ± 0.40 |
| Month 3 | 0 ± 0 | 0.0270 ± 0.0081 | 0.108 ± 0.074 | 0.326 ± 0.109 |
| Month 12 | 0 ± 0 | 0.0179 ± 0.0358 | 0.0220 ± 0.0334 | 0.267 ± 0.129 |
| Month 18 | 0 ± 0 | 0.00829 ± 0.00762 | 0.0564 ± 0.0213 | 0.236 ± 0.072 |
| *p*-Nitrobenzoic acid (mg/24 hours) | | | | |
| Week 2 | 0 ± 0 | 0.137 | 0.144 ± 0.103 | 0.130 ± 0.077 |
| Month 3 | 0 ± 0 | 0.0794 ± 0.0404 | 0.160 ± 0.144 | 0.678 ± 0.917 |
| Month 12 | 0 ± 0 | 0.0155 ± 0.0309 | 0.0472 ± 0.0388 | 0.340 ± 0.225 |
| Month 18 | 0 ± 0 | 0 ± 0 | 0.130 ± 0.131 | 0.431 ± 0.245 |
| *p*-Nitrobenzoic acid/creatinine ratio | | | | |
| Week 2 | 0 ± 0 | 0.513 | 1.34 ± 0.74 | 3.25 ± 0.67 |
| Month 3 | 0 ± 0 | 0.253 ± 0.028 | 1.20 ± 0.71 | 2.58 ± 1.06 |
| Month 12 | 0 ± 0 | 0.0472 ± 0.0943 | 0.137 ± 0.118 | 0.931 ± 0.571 |
| Month 18 | 0 ± 0 | 0 ± 0 | 0.217 ± 0.207 | 0.907 ± 0.491 |

[a] Data are presented as mean ± standard error.

# APPENDIX G
# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

## Procurement and Characterization of *p*-Nitrotoluene

*p*-Nitrotoluene was obtained from SAF Bulk Chemicals (St. Louis, MO) in one lot (338297/1495). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and the study laboratory. Reports on analyses performed in support of the *p*-nitrotoluene studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, pale yellow, crystalline solid, was identified as *p*-nitrotoluene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and low-resolution mass spectrometry at the analytical chemistry laboratory, as well as by infrared and nuclear magnetic resonance spectroscopy at the study laboratory. All spectra were consistent with the literature spectra (*Registry of Mass Spectral Data,* 1974; *Sadtler,* 1979; *Aldrich,* 1981; *Handbook of Proton NMR Spectra and Data,* 1985) and with the structure of *p*-nitrotoluene. The infrared and nuclear magnetic resonance spectra are presented in Figures G1 and G2. In addition, the analytical chemistry laboratory analyzed the chemical with high-resolution mass spectrometry; the observed mass of the parent ion was within acceptable limits.

The purity of lot 338297/1495 was determined by Karl Fischer water analysis and by gas chromatography using systems A and B (Table G1). The study laboratory performed gas chromatography using system C, with acetophenone added as an internal standard.

Karl Fischer water analysis indicated 0.694% water. Gas chromatography by system A indicated one major peak and one minor peak accounting for 0.26% of the total integrated area. System B indicated one major peak and one minor peak accounting for 0.22% of the total integrated area. Gas chromatography by system C indicated one major peak and one impurity with an area of 0.1% or less relative to the major peak area. The overall purity was determined to be greater than 99%.

Stability studies of lot 23 of the bulk chemical (not used in the current studies) were performed by Midwest Research Institute (Kansas City, MO) using gas chromatography by system D with hexadecane added as an internal standard. No degradation of the bulk chemical was observed after storage for 2 weeks, protected from light, at up to 60° C. To ensure stability, the bulk chemical was stored in the dark at approximately 5° C in sealed containers. Stability was monitored during the studies by the study laboratory by gas chromatography using a system similar to system C. No degradation of the bulk chemical was detected.

## Preparation and Analysis of Dose Formulations

The dose formulations were prepared every 2 weeks by mixing *p*-nitrotoluene with feed (Table G2). A premix was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for 15 minutes using an intensifier bar for the initial 5 minutes. Formulations were stored with minimal head space in doubled, opaque plastic bags inside covered plastic buckets at approximately 5° C for up to 35 days.

Stability studies of the 1,250 ppm dose formulation and homogeneity studies of the 1,250 and 5,000 ppm dose formulations in nonirradiated NTP-2000 diet were performed by the analytical chemistry laboratory using gas chromatography (system E). Homogeneity was confirmed, and the stability of the dose formulations was confirmed for 35 days when stored in the dark at temperatures up to 3° C. However, samples stored at room temperature, open to air and light, for 7 days were not stable. Losses were shown to be due to volatility. The initial batch of dose formulations was prepared to be within 10% of the target concentrations. However, due to the volatile losses during formulation, the study laboratory prepared dose formulations at concentrations up to 115% of

the target concentrations thereafter. Dose formulations were replaced in animal room feeders on a 2-day, 2-day, 3-day schedule. The study laboratory also confirmed the homogeneity of the 1,250 and 5,000 ppm dose formulations using gas chromatography (system F). After the change to irradiated feed, the study laboratory performed additional analyses with gas chromatography (system E) to compare the homogeneity of dose formulations prepared with nonirradiated feed to that of dose formulations prepared with irradiated feed. The homogeneity of all samples was confirmed; relative standard deviations ranged from 1.1% to 3.3% for samples prepared with nonirradiated feed and from 0.8% to 1.1% for samples prepared with irradiated feed.

Analyses of the dose formulations of *p*-nitrotoluene were conducted by the study laboratory every 8 to 12 weeks using gas chromatography by system F (Table G3). Of the dose formulations analyzed and used, all 248 had concentrations that were 90% to 115% of the target concentration; animal room sample concentrations ranged from 74% to 101% of the target concentration.

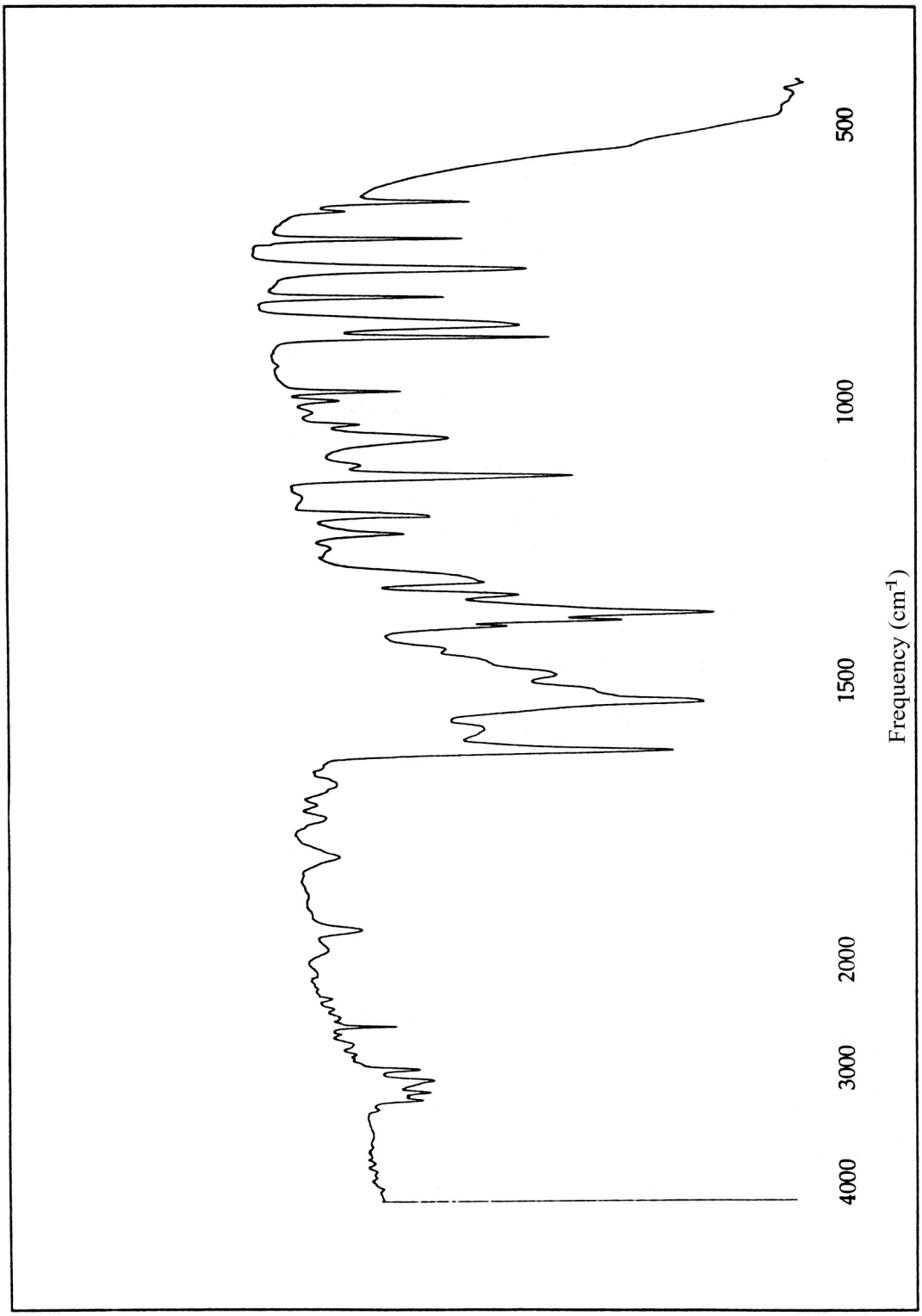


**FIGURE G1**
**Infrared Absorption Spectrum of *p*-Nitrotoluene**

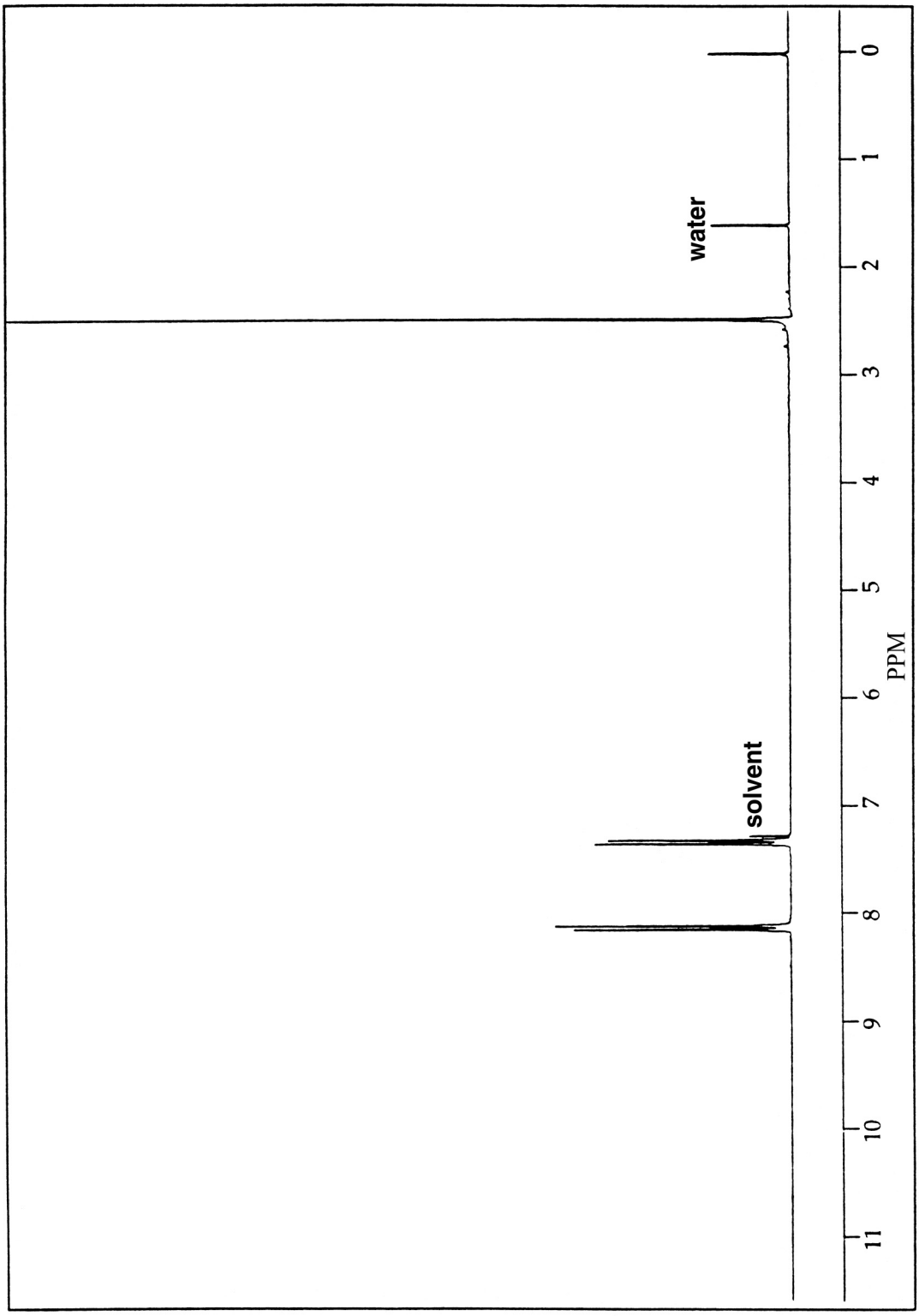


**FIGURE G2**
**Nuclear Magnetic Resonance Spectrum of *p*-Nitrotoluene**

**TABLE G1**
**Gas Chromatography Systems Used in the 2-Year Feed Studies of *p*-Nitrotoluene[a]**

| Detection System | Column | Carrier Gas | Oven Temperature Program |
|---|---|---|---|
| **System A** | | | |
| Flame ionization | SE-30, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific, Folsom, CA) | Helium at 1 mL/minute | 50° C to 250° C at 5° C/minute |
| **System B** | | | |
| Flame ionization | DB-17, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific) | Helium at 1 mL/minute | 50° C to 250° C at 5° C/minute |
| **System C** | | | |
| Flame ionization | Rtx-5, 30 m × 0.53 mm, 1-µm film (Restek, Bellefonte, PA) | Helium at approximately 12 mL/minute | 100° C for 5 minutes, then 70° C/minute to 120° C held for 4 minutes |
| **System D** | | | |
| Flame ionization | 10% Carbowax 20M-TPA on 80/100 Chromosorb W (AW), 1.8 m × 4 mm | Nitrogen at 70 mL/minute | Isothermal at 190° C |
| **System E** | | | |
| Flame ionization | SE-30, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific) | Nitrogen at 1 mL/minute | 120° C for 7 minutes, then 30° C/minute to 300° C, held for 7 minutes |
| **System F** | | | |
| Flame ionization | Rtx-5, 30 m × 0.53 mm, 1-µm film (Restek) | Helium at approximately 12 mL/minute | 100° C for 5 minutes, then 70° C/minute to 290° C held for 20 minutes |

[a] Gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA) and Varian, Inc. (Palo Alto, CA) (system D).

## TABLE G2
## Preparation and Storage of Dose Formulations in the 2-Year Feed Studies of *p*-Nitrotoluene

**Preparation**
A premix of feed and *p*-nitrotoluene was prepared, then layered with the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Dose formulations were prepared with irradiated feed beginning July 15, 1996. Dose formulations were prepared every 2 weeks.

**Chemical Lot Number**
338297/1495

**Maximum Storage Time**
35 days

**Storage Conditions**
Stored in doubled, opaque plastic bags inside covered plastic buckets at approximately 5° C

**Study Laboratory**
Southern Research Institute (Birmingham, AL)

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration[a] (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| November 6, 1995[b] | November 6-7, 1995 | 1,250 | 1,380 | +10 |
| | | 1,250 | 1,170 | –6 |
| | | 2,500 | 2,530 | +1 |
| | | 2,500 | 2,580 | +3 |
| | | 5,000 | 5,450 | +9 |
| | | 5,000 | 5,290 | +6 |
| | November 29, 1995[c] | 1,250 | 1,030 | –18 |
| | | 2,500 | 1,970 | –21 |
| | | 5,000 | 3.750 | –25 |
| November 20-21, 1995 | November 20-21, 1995 | 1,250 | 1,390[d] | +11 |
| | | 1,250 | 1,300 | +4 |
| | | 1,250 | 1,390[d] | +11 |
| | | 1,250 | 1,360 | +9 |
| | | 1,250 | 1,340 | +7 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,350 | +8 |
| | | 2,500 | 2,660 | +6 |
| | | 2,500 | 2,750 | +10 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,690 | +8 |
| | | 2,500 | 2,640 | +6 |
| | | 2,500 | 2,690 | +8 |
| | | 2,500 | 2,660 | +6 |
| | | 5,000 | 5,230 | +5 |
| | | 5,000 | 5,250 | +5 |
| | | 5,000 | 5,150 | +3 |
| | | 5,000 | 5,460 | +9 |
| | | 5,000 | 5,370 | +7 |
| | | 5,000 | 5,320 | +6 |
| | | 5,000 | 5,450 | +9 |
| | December 14-15, 1995[c] | 1,250 | 1,100 | –12 |
| | | 2,500 | 2,130 | –15 |
| | | 2,500 | 2,250 | –10 |
| | | 5,000 | 4,390 | –12 |
| November 22, 1995 | November 22, 1995 | 1,250 | 1,320[e] | +6 |
| | | 1,250 | 1,370[e] | +10 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| January 17-18, 1996 | January 18-19, 1996 | 1,250 | 1,350 | +8 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,330 | +6 |
| | | 1,250 | 1,370 | +10 |
| | | 1,250 | 1,370 | +10 |
| | | 2,500 | 2,580 | +3 |
| | | 2,500 | 2,710 | +8 |
| | | 2,500 | 2,660 | +6 |
| | | 2,500 | 2,590 | +4 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,510 | 0 |
| | | 2,500 | 2,640 | +6 |
| | | 5,000 | 5,310 | +6 |
| | ` | 5,000 | 5,340 | +7 |
| | | 5,000 | 5,150 | +3 |
| | | 5,000 | 5,280 | +6 |
| | | 5,000 | 5,390 | +8 |
| | | 5,000 | 5,100 | +2 |
| | | 5,000 | 5,220 | +4 |
| March 25-26, 1996 | March 26-27, 1996 | 1,250 | 1,340 | +7 |
| | | 1,250 | 1,350 | +8 |
| | | 1,250 | 1,390 | +11 |
| | | 1,250 | 1,390 | +11 |
| | | 1,250 | 1,400 | +12 |
| | | 1,250 | 1,370 | +10 |
| | | 1,250 | 1,410 | +13 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,610 | +4 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,600 | +4 |
| | | 2,500 | 2,580 | +3 |
| | | 2,500 | 2,460 | –2 |
| | | 2,500 | 2,570 | +3 |
| | | 5,000 | 5,080 | +2 |
| | | 5,000 | 5,210 | +4 |
| | | 5,000 | 5,060 | +1 |
| | | 5,000 | 5,180 | +4 |
| | | 5,000 | 5,390 | +8 |
| | | 5,000 | 5,310 | +6 |
| | | 5,000 | 5,380 | +8 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| June 17-18, 1996 | June 18-19, 1996 | 1,250 | 1,230 | –2 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,290 | +3 |
| | | 1,250 | 1,340 | +7 |
| | | 1,250 | 1,340 | +7 |
| | | 1,250 | 1,300 | +4 |
| | | 1,250 | 1,340 | +7 |
| | | 2,500 | 2,610 | +4 |
| | | 2,500 | 2,650 | +6 |
| | | 2,500 | 2,650 | +6 |
| | | 2,500 | 2,600 | +4 |
| | | 2,500 | 2,510 | 0 |
| | | 2,500 | 2,470 | –1 |
| | | 2,500 | 2,540 | +2 |
| | | 5,000 | 5,030 | +1 |
| | | 5,000 | 5,130 | +3 |
| | | 5,000 | 5,320 | +6 |
| | | 5,000 | 5,030 | +1 |
| | | 5,000 | 5,010 | 0 |
| | | 5,000 | 5,200 | +4 |
| | | 5,000 | 4,950 | –1 |
| | July 16-17, 1996[c] | 1,250 | 972 | –22 |
| | | 1,250 | 1,100 | –12 |
| | | 2,500 | 1,840 | –26 |
| | | 2,500 | 2,010 | –20 |
| | | 5,000 | 4,220 | –16 |
| | | 5,000 | 3,690 | –26 |
| July 15-16, 1996 | July 16-19, 1996 | 1,250 | 1,370 | +10 |
| | | 1,250 | 1,330 | +6 |
| | | 1,250 | 1,370 | +10 |
| | | 1,250 | 1,290 | +3 |
| | | 1,250 | 1,240 | –1 |
| | | 1,250 | 1,270 | +2 |
| | | 1,250 | 1,250 | 0 |
| | | 1,250 | 1,220 | –2 |
| | | 2,500 | 2,540 | +2 |
| | | 2,500 | 2,500 | 0 |
| | | 2,500 | 2,590 | +4 |
| | | 2,500 | 2,550 | +2 |
| | | 2,500 | 2,680 | +7 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,530 | +1 |
| | | 2,500 | 2,510 | 0 |
| | | 5,000 | 5,360 | +7 |
| | | 5,000 | 5,110 | +2 |
| | | 5,000 | 5,040 | +1 |
| | | 5,000 | 5,240 | +5 |
| | | 5,000 | 5,060 | +1 |
| | | 5,000 | 5,200 | +4 |
| | | 5,000 | 5,200 | +4 |
| | | 5,000 | 5,300 | +6 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| October 7-8, 1996 | October 8-10, 1996 | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,290 | +3 |
| | | 1,250 | 1,270 | +2 |
| | | 1,250 | 1,270 | +2 |
| | | 1,250 | 1,270 | +2 |
| | | 1,250 | 1,280 | +2 |
| | | 1,250 | 1,300 | +4 |
| | | 2,500 | 2,700 | +8 |
| | | 2,500 | 2,650 | +6 |
| | | 2,500 | 2,490 | 0 |
| | | 2,500 | 2,550 | +2 |
| | | 2,500 | 2,350 | –6 |
| | | 2,500 | 2,510 | 0 |
| | | 2,500 | 2,580 | +3 |
| | | 5,000 | 5,130 | +3 |
| | | 5,000 | 5,090 | +2 |
| | | 5,000 | 5,240 | +5 |
| | | 5,000 | 5,170 | +3 |
| | | 5,000 | 5,090 | +2 |
| | | 5,000 | 5,360 | +7 |
| | | 5,000 | 5,230 | +5 |
| December 17, 1996 | December 17-18, 1996 | 1,250 | 1,360 | +9 |
| | | 1,250 | 1,420 | +14 |
| | | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,410 | +13 |
| | | 1,250 | 1,170[f] | –6 |
| | | 1,250 | 1,320 | +6 |
| | | 2,500 | 2,690 | +8 |
| | | 2,500 | 2,750 | +10 |
| | | 2,500 | 2,730 | +9 |
| | | 2,500 | 2,570 | +3 |
| | | 2,500 | 2,820 | +13 |
| | | 2,500 | 2,700 | +8 |
| | | 2,500 | 2,710 | +8 |
| | | 5,000 | 5,180 | +4 |
| | | 5,000 | 6,180[d] | +24 |
| | | 5,000 | 5,050 | +1 |
| | | 5,000 | 5,140 | +3 |
| | | 5,000 | 5,320 | +6 |
| | | 5,000 | 5,210 | +4 |
| | | 5,000 | 5,250 | +5 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| December 30, 1996 | December 30, 1996 | 1,250 | 1,300[e] | +4 |
| | | 5,000 | 5,510[e] | +10 |
| February 25-26, 1997 | February 26-28, 1997 | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,300 | +4 |
| | | 2,500 | 2,610 | +4 |
| | | 2,500 | 2,540 | +2 |
| | | 2,500 | 2,530 | +1 |
| | | 2,500 | 2,570 | +3 |
| | | 2,500 | 2,630 | +5 |
| | | 2,500 | 2,560 | +2 |
| | | 2,500 | 2,520 | +1 |
| | | 5,000 | 5,410 | +8 |
| | | 5,000 | 5,290 | +6 |
| | | 5,000 | 5,230 | +5 |
| | | 5,000 | 5,390 | +8 |
| | | 5,000 | 5,330 | +7 |
| | | 5,000 | 5,250 | +5 |
| | | 5,000 | 5,430 | +9 |
| | March 18-19, 1997[c] | 1,250 | 1,200 | –4 |
| | | 1,250 | 1,080 | –14 |
| | | 2,500 | 2,080 | –17 |
| | | 2,500 | 2,480 | –1 |
| | | 5,000 | 4,430 | –11 |
| | | 5,000 | 5,070 | +1 |
| May 6, 1997 | May 6-8, 1997 | 1,250 | 1,390 | +11 |
| | | 1,250 | 1,240 | –1 |
| | | 1,250 | 1,360 | +9 |
| | | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,280 | +2 |
| | | 1,250 | 1,290 | +3 |
| | | 1,250 | 1,330 | +6 |
| | | 2,500 | 2,680 | +7 |
| | | 2,500 | 2,580 | +3 |
| | | 2,500 | 2,760 | +10 |
| | | 2,500 | 2,560 | +2 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,640 | +6 |
| | | 2,500 | 2,540 | +2 |
| | | 5,000 | 5,130 | +3 |
| | | 5,000 | 5,240 | +5 |
| | | 5,000 | 5,570 | +11 |
| | | 5,000 | 5,280 | +6 |
| | | 5,000 | 5,390 | +8 |
| | | 5,000 | 5,300 | +6 |
| | | 5,000 | 5,120 | +2 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| July 28-29, 1997 | July 29-August 1, 1997 | 1,250 | 1,250 | 0 |
| | | 1,250 | 1,250 | 0 |
| | | 1,250 | 1,300 | +4 |
| | | 1,250 | 1,270 | +2 |
| | | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,350 | +8 |
| | | 1,250 | 1,290 | +3 |
| | | 2,500 | 2,730 | +9 |
| | | 2,500 | 2,710 | +8 |
| | | 2,500 | 2,620 | +5 |
| | | 2,500 | 2,630 | +5 |
| | | 2,500 | 2,600 | +4 |
| | | 2,500 | 2,680 | +7 |
| | | 2,500 | 2,880[d] | +15 |
| | | 5,000 | 5,310 | +6 |
| | | 5,000 | 5,080 | +2 |
| | | 5,000 | 4,950 | –1 |
| | | 5,000 | 5,230 | +5 |
| | | 5,000 | 5,930[d] | +19 |
| | | 5,000 | 5,390 | +8 |
| | | 5,000 | 5,080 | +2 |
| August 4, 1997 | August 4-5, 1997 | 2,500 | 2,710[e] | +8 |
| | | 5,000 | 5,410[e] | +8 |
| September 22-23, 1997 | September 23-25, 1997 | 1,250 | 1,320 | +6 |
| | | 1,250 | 1,300 | +4 |
| | | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,310 | +5 |
| | | 1,250 | 1,280 | +2 |
| | | 1,250 | 1,330 | +6 |
| | | 1,250 | 1,340 | +7 |
| | | 2,500 | 2,940[g] | +18 |
| | | 2,500 | 2,650 | +6 |
| | | 2,500 | 2,640 | +6 |
| | | 2,500 | 2,610 | +4 |
| | | 2,500 | 2,580 | +3 |
| | | 2,500 | 2,580 | +3 |
| | | 2,500 | 2,650 | +6 |
| | | 5,000 | 5,240 | +5 |
| | | 5,000 | 5,150 | +3 |
| | | 5,000 | 5,160 | +3 |
| | | 5,000 | 5,240 | +5 |
| | | 5,000 | 5,350 | +7 |
| | | 5,000 | 5,310 | +6 |
| | | 5,000 | 5,130 | +3 |
| | October 13-15, 1997[c] | 1,250 | 1,050 | –16 |
| | | 1,250 | 1,230 | –2 |
| | | 2,500 | 2,000 | –20 |
| | | 2,500 | 2,480 | –1 |
| | | 5,000 | 4,140 | –17 |
| | | 5,000 | 5,070 | +1 |

**TABLE G3**
**Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrotoluene**

| Date Prepared | Date Analyzed | Target Concentration (ppm) | Determined Concentration (ppm) | Difference from Target (%) |
|---|---|---|---|---|
| November 18, 1997 | November 19-20, 1997 | 1,250 | 1,260 | +1 |
| | | 1,250 | 1,380 | +10 |
| | | 1,250 | 1,320 | +6 |
| | | 2,500 | 2,720 | +9 |
| | | 2,500 | 2,660 | +6 |
| | | 2,500 | 2,710 | +8 |
| | | 5,000 | 5,270 | +5 |
| | | 5,000 | 5,440 | +9 |
| | | 5,000 | 5,410 | +8 |

[a] Results of duplicate analyses
[b] Dose formulations were administered to mice only.
[c] Animal room samples
[d] Remixed; not used in study
[e] Results of remix
[f] Duplicate and triplicate analyses indicated expected/observed values less than expected; dose formulation was remixed.
[g] Not used in study

# APPENDIX H
# FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF *p*-NITROTOLUENE

**TABLE H1**
**Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Feed (g/day)[a] | Body Weight (g) | Feed (g/day) | Body Weight (g) | Dose (mg/kg)[b] | Feed (g/day) | Body Weight (g) | Dose (mg/kg) | Feed (g/day) | Body Weight (g) | Dose (mg/kg) |
| 4 | 19.4 | 206 | 18.9 | 200 | 118 | 18.6 | 196 | 236 | 18.8 | 181 | 521 |
| 8 | 18.1 | 282 | 18.1 | 273 | 83 | 17.8 | 270 | 165 | 17.9 | 246 | 363 |
| 12 | 17.4 | 324 | 17.0 | 319 | 67 | 17.5 | 310 | 141 | 17.4 | 283 | 308 |
| 16 | 18.4 | 352 | 17.8 | 342 | 65 | 18.1 | 336 | 135 | 18.0 | 303 | 297 |
| 20 | 17.1 | 377 | 16.8 | 365 | 58 | 16.8 | 359 | 117 | 16.3 | 322 | 254 |
| 24 | 17.8 | 390 | 17.0 | 381 | 56 | 16.8 | 368 | 114 | 16.0 | 335 | 239 |
| 28 | 17.5 | 405 | 16.9 | 392 | 54 | 17.1 | 384 | 111 | 16.5 | 343 | 240 |
| 32 | 16.5 | 421 | 16.1 | 404 | 50 | 17.0 | 394 | 108 | 16.4 | 352 | 233 |
| 36 | 16.7 | 422 | 16.6 | 410 | 51 | 16.5 | 403 | 103 | 15.6 | 362 | 216 |
| 40 | 17.0 | 426 | 16.7 | 414 | 51 | 16.3 | 405 | 100 | 15.9 | 361 | 220 |
| 44 | 16.2 | 433 | 15.9 | 422 | 47 | 15.9 | 410 | 97 | 15.4 | 368 | 209 |
| 48 | 15.9 | 436 | 15.2 | 426 | 45 | 15.3 | 418 | 92 | 14.1 | 370 | 191 |
| 52 | 15.5 | 438 | 15.6 | 427 | 46 | 15.4 | 419 | 92 | 15.2 | 374 | 203 |
| 56 | 17.4 | 435 | 16.6 | 423 | 49 | 16.6 | 415 | 100 | 15.5 | 373 | 208 |
| 60 | 16.4 | 437 | 16.5 | 430 | 48 | 16.1 | 419 | 96 | 16.2 | 378 | 214 |
| 64 | 16.6 | 440 | 16.1 | 432 | 47 | 16.0 | 425 | 94 | 14.9 | 381 | 196 |
| 68 | 16.1 | 439 | 15.3 | 431 | 44 | 15.7 | 427 | 92 | 15.3 | 381 | 200 |
| 72 | 16.0 | 438 | 15.6 | 428 | 46 | 16.1 | 425 | 95 | 16.2 | 385 | 211 |
| 76 | 16.6 | 440 | 16.3 | 437 | 47 | 16.2 | 432 | 94 | 15.2 | 390 | 195 |
| 80 | 15.9 | 444 | 15.9 | 437 | 45 | 15.5 | 433 | 89 | 15.2 | 390 | 196 |
| 84 | 15.6 | 434 | 15.7 | 434 | 45 | 15.3 | 430 | 89 | 15.3 | 387 | 198 |
| 88 | 15.3 | 432 | 15.0 | 428 | 44 | 14.6 | 424 | 86 | 14.4 | 385 | 187 |
| 92 | 15.6 | 425 | 15.2 | 426 | 45 | 14.8 | 417 | 89 | 15.3 | 381 | 200 |
| 96 | 16.2 | 419 | 15.9 | 420 | 47 | 15.5 | 412 | 94 | 15.6 | 380 | 205 |
| 100 | 13.7 | 410 | 15.3 | 415 | 46 | 14.1 | 409 | 86 | 14.6 | 374 | 195 |
| 104 | 14.5 | 402 | 14.6 | 409 | 44 | 14.0 | 402 | 87 | 13.8 | 366 | 189 |
| **Mean for weeks** | | | | | | | | | | | |
| 4-13 | 18.3 | 271 | 18.0 | 264 | 89 | 18.0 | 259 | 181 | 18.0 | 236 | 397 |
| 14-52 | 16.9 | 410 | 16.5 | 398 | 52 | 16.5 | 390 | 107 | 16.0 | 349 | 230 |
| 53-104 | 15.8 | 430 | 15.7 | 427 | 46 | 15.4 | 421 | 92 | 15.2 | 381 | 199 |

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p*-nitrotoluene consumed per kilogram body weight per day

**TABLE H2**
**Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Feed (g/day)[a] | Body Weight (g) | Feed (g/day) | Body Weight (g) | Dose (mg/kg)[b] | Feed (g/day) | Body Weight (g) | Dose (mg/kg) | Feed (g/day) | Body Weight (g) | Dose (mg/kg) |
| 4 | 12.4 | 144 | 12.4 | 141 | 110 | 12.0 | 140 | 214 | 12.4 | 134 | 462 |
| 8 | 11.5 | 168 | 11.6 | 166 | 88 | 11.5 | 164 | 176 | 11.5 | 156 | 370 |
| 12 | 10.6 | 182 | 10.6 | 179 | 74 | 10.7 | 176 | 152 | 11.2 | 167 | 336 |
| 16 | 11.5 | 192 | 11.1 | 188 | 74 | 11.3 | 185 | 153 | 11.3 | 173 | 327 |
| 20 | 10.7 | 198 | 10.3 | 194 | 66 | 10.2 | 191 | 134 | 10.5 | 182 | 289 |
| 24 | 10.1 | 204 | 10.4 | 200 | 65 | 9.8 | 196 | 125 | 10.2 | 185 | 276 |
| 28 | 10.8 | 211 | 10.6 | 207 | 64 | 10.2 | 201 | 127 | 10.2 | 189 | 269 |
| 32 | 10.6 | 220 | 10.0 | 209 | 60 | 9.8 | 206 | 118 | 10.3 | 194 | 266 |
| 36 | 10.6 | 223 | 10.0 | 216 | 58 | 10.2 | 212 | 120 | 9.8 | 198 | 247 |
| 40 | 10.9 | 224 | 10.5 | 216 | 61 | 10.1 | 213 | 119 | 9.8 | 196 | 252 |
| 44 | 10.5 | 232 | 9.9 | 222 | 56 | 9.9 | 216 | 115 | 9.6 | 198 | 243 |
| 48 | 10.1 | 234 | 9.6 | 224 | 53 | 9.0 | 218 | 103 | 8.4 | 198 | 211 |
| 52 | 11.2 | 236 | 10.3 | 227 | 57 | 10.0 | 220 | 114 | 9.7 | 201 | 242 |
| 56 | 11.4 | 243 | 10.9 | 231 | 59 | 10.6 | 225 | 118 | 9.9 | 201 | 248 |
| 60 | 10.9 | 250 | 11.0 | 236 | 58 | 10.7 | 226 | 118 | 10.1 | 202 | 251 |
| 64 | 11.5 | 258 | 11.0 | 239 | 57 | 10.5 | 232 | 113 | 9.8 | 203 | 242 |
| 68 | 11.4 | 263 | 11.0 | 249 | 55 | 10.9 | 238 | 114 | 9.8 | 206 | 237 |
| 72 | 12.1 | 270 | 11.3 | 253 | 56 | 10.8 | 241 | 112 | 9.9 | 207 | 240 |
| 76 | 11.7 | 277 | 11.3 | 260 | 54 | 11.3 | 249 | 113 | 9.6 | 208 | 231 |
| 80 | 12.2 | 285 | 11.5 | 267 | 54 | 11.4 | 257 | 110 | 10.0 | 213 | 236 |
| 84 | 12.3 | 288 | 11.7 | 268 | 55 | 11.0 | 261 | 106 | 10.2 | 212 | 241 |
| 88 | 12.0 | 293 | 11.0 | 269 | 51 | 10.9 | 262 | 104 | 9.9 | 210 | 235 |
| 92 | 11.3 | 295 | 11.1 | 272 | 51 | 10.5 | 262 | 101 | 10.3 | 212 | 243 |
| 96 | 12.8 | 293 | 11.9 | 269 | 55 | 11.6 | 262 | 111 | 10.2 | 211 | 241 |
| 100 | 11.6 | 293 | 11.8 | 272 | 54 | 11.6 | 266 | 109 | 9.5 | 212 | 225 |
| 104 | 11.7 | 294 | 11.2 | 272 | 51 | 11.4 | 267 | 107 | 9.6 | 210 | 230 |
| **Mean for weeks** | | | | | | | | | | | |
| 4-13 | 11.5 | 165 | 11.5 | 162 | 91 | 11.4 | 160 | 181 | 11.7 | 152 | 389 |
| 14-52 | 10.7 | 217 | 10.3 | 210 | 61 | 10.1 | 206 | 123 | 10.0 | 191 | 262 |
| 53-104 | 11.8 | 277 | 11.3 | 258 | 55 | 11.0 | 250 | 110 | 9.9 | 208 | 238 |

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p*-nitrotoluene consumed per kilogram body weight per day

**TABLE H3**
**Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| Week | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Feed (g/day)[a] | Body Weight (g) | Feed (g/day) | Body Weight (g) | Dose (mg/kg)[b] | Feed (g/day) | Body Weight (g) | Dose (mg/kg) | Feed (g/day) | Body Weight (g) | Dose (mg/kg) |
| 4 | 6.2 | 24.4 | 5.9 | 24.3 | 304 | 5.9 | 24.4 | 606 | 5.4 | 23.8 | 1,139 |
| 8 | 5.5 | 27.9 | 5.4 | 27.5 | 246 | 5.1 | 27.7 | 464 | 5.1 | 26.9 | 947 |
| 12 | 5.6 | 31.6 | 5.6 | 31.3 | 222 | 5.5 | 31.5 | 433 | 5.2 | 30.3 | 866 |
| 16 | 5.3 | 34.8 | 5.3 | 34.5 | 193 | 5.1 | 34.4 | 368 | 5.0 | 33.1 | 750 |
| 20 | 5.3 | 37.7 | 5.6 | 37.5 | 188 | 5.7 | 37.3 | 380 | 5.4 | 35.8 | 757 |
| 24 | 5.6 | 39.4 | 5.3 | 39.0 | 171 | 5.4 | 38.7 | 349 | 5.2 | 36.9 | 711 |
| 28 | 5.1 | 40.8 | 4.9 | 40.7 | 152 | 4.9 | 40.1 | 306 | 4.8 | 39.0 | 614 |
| 32 | 5.1 | 42.4 | 5.1 | 42.2 | 152 | 5.0 | 41.7 | 299 | 5.0 | 40.7 | 612 |
| 36 | 4.7 | 43.0 | 5.0 | 43.1 | 144 | 4.9 | 42.1 | 292 | 4.9 | 41.3 | 590 |
| 40 | 5.7 | 43.8 | 5.6 | 43.7 | 160 | 5.5 | 43.1 | 322 | 5.1 | 41.3 | 620 |
| 44 | 5.3 | 44.7 | 5.1 | 44.9 | 142 | 5.1 | 44.0 | 293 | 5.0 | 41.9 | 597 |
| 48 | 5.6 | 45.4 | 5.8 | 44.8 | 162 | 5.8 | 43.9 | 328 | 5.6 | 42.3 | 662 |
| 52 | 6.1 | 45.2 | 6.0 | 44.7 | 169 | 6.0 | 43.4 | 345 | 5.8 | 42.1 | 684 |
| 56 | 5.5 | 45.8 | 5.7 | 45.5 | 156 | 5.5 | 44.4 | 310 | 5.5 | 42.5 | 643 |
| 60 | 5.6 | 45.8 | 5.7 | 45.9 | 156 | 5.8 | 44.0 | 327 | 5.6 | 42.1 | 670 |
| 64 | 5.4 | 47.1 | 5.6 | 47.3 | 147 | 5.4 | 45.1 | 301 | 5.3 | 43.1 | 618 |
| 68 | 5.3 | 47.4 | 5.5 | 47.7 | 145 | 5.5 | 45.6 | 304 | 5.1 | 43.1 | 592 |
| 72 | 5.0 | 46.8 | 5.1 | 47.1 | 135 | 5.2 | 45.4 | 289 | 5.0 | 42.4 | 595 |
| 76 | 5.7 | 45.5 | 5.8 | 46.6 | 154 | 5.9 | 44.5 | 333 | 5.5 | 42.5 | 647 |
| 80 | 5.5 | 46.3 | 5.5 | 47.2 | 146 | 5.3 | 45.2 | 294 | 5.0 | 42.8 | 588 |
| 84 | 5.2 | 46.7 | 5.4 | 47.5 | 142 | 5.3 | 45.4 | 291 | 5.1 | 42.4 | 606 |
| 88 | 5.8 | 45.5 | 5.8 | 46.0 | 158 | 5.7 | 44.4 | 320 | 5.4 | 42.1 | 645 |
| 92 | 5.6 | 45.1 | 5.9 | 45.4 | 161 | 5.8 | 43.9 | 331 | 5.4 | 42.0 | 641 |
| 96 | 6.2 | 43.0 | 6.1 | 42.3 | 182 | 6.2 | 40.5 | 382 | 5.8 | 39.0 | 745 |
| 100 | 5.6 | 41.7 | 5.6 | 40.3 | 174 | 5.5 | 38.8 | 353 | 5.1 | 37.5 | 681 |
| 104 | 5.3 | 41.3 | 5.4 | 39.7 | 170 | 5.2 | 37.3 | 348 | 4.7 | 36.2 | 655 |
| **Mean for weeks** | | | | | | | | | | | |
| 4-13 | 5.7 | 27.9 | 5.6 | 27.7 | 257 | 5.5 | 27.9 | 501 | 5.3 | 27.0 | 984 |
| 14-52 | 5.4 | 41.7 | 5.4 | 41.5 | 163 | 5.3 | 40.9 | 328 | 5.2 | 39.5 | 660 |
| 53-104 | 5.5 | 45.2 | 5.6 | 45.3 | 156 | 5.6 | 43.4 | 322 | 5.3 | 41.4 | 640 |

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p*-nitrotoluene consumed per kilogram body weight per day

**TABLE H4**
**Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *p*-Nitrotoluene**

| | 0 ppm | | 1,250 ppm | | | 2,500 ppm | | | 5,000 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Feed (g/day)[a] | Body Weight (g) | Feed (g/day) | Body Weight (g) | Dose (mg/kg)[b] | Feed (g/day) | Body Weight (g) | Dose (mg/kg) | Feed (g/day) | Body Weight (g) | Dose (mg/kg) |
| 4 | 3.5 | 18.1 | 3.9 | 19.2 | 257 | 4.0 | 19.3 | 520 | 3.7 | 18.4 | 1,002 |
| 8 | 3.8 | 21.7 | 3.9 | 22.4 | 216 | 3.9 | 22.2 | 435 | 3.7 | 20.9 | 883 |
| 12 | 4.1 | 25.1 | 4.1 | 26.5 | 196 | 4.2 | 25.9 | 401 | 3.9 | 23.3 | 834 |
| 16 | 4.1 | 28.2 | 4.0 | 28.2 | 179 | 4.2 | 27.9 | 372 | 3.8 | 24.7 | 768 |
| 20 | 4.0 | 30.8 | 3.9 | 29.9 | 162 | 4.1 | 30.1 | 344 | 3.9 | 26.4 | 739 |
| 24 | 4.1 | 32.2 | 4.4 | 32.8 | 166 | 4.1 | 33.0 | 314 | 3.7 | 28.2 | 659 |
| 28 | 3.9 | 34.2 | 3.9 | 34.6 | 143 | 3.9 | 33.8 | 290 | 3.8 | 28.7 | 654 |
| 32 | 4.1 | 34.7 | 4.0 | 36.4 | 137 | 3.7 | 34.8 | 266 | 3.8 | 29.7 | 631 |
| 36 | 4.0 | 36.3 | 4.1 | 37.4 | 135 | 3.9 | 36.5 | 265 | 3.7 | 31.1 | 603 |
| 40 | 4.4 | 36.2 | 4.3 | 38.0 | 143 | 4.4 | 37.2 | 296 | 3.9 | 31.6 | 621 |
| 44 | 4.4 | 36.2 | 4.5 | 38.5 | 145 | 4.1 | 36.9 | 277 | 4.2 | 32.2 | 648 |
| 48 | 5.1 | 38.9 | 5.0 | 40.8 | 153 | 4.7 | 39.7 | 298 | 4.3 | 33.6 | 637 |
| 52 | 4.3 | 38.5 | 4.3 | 39.2 | 138 | 4.3 | 39.4 | 276 | 4.2 | 33.2 | 629 |
| 56 | 4.5 | 38.4 | 4.4 | 39.7 | 139 | 4.4 | 39.5 | 280 | 4.1 | 33.5 | 607 |
| 60 | 4.4 | 37.9 | 4.8 | 39.0 | 152 | 4.8 | 38.5 | 311 | 4.5 | 33.6 | 668 |
| 64 | 4.2 | 39.0 | 4.4 | 41.2 | 135 | 4.2 | 40.0 | 260 | 3.8 | 34.9 | 539 |
| 68 | 4.4 | 39.1 | 4.5 | 41.6 | 134 | 4.4 | 40.8 | 272 | 4.0 | 34.6 | 582 |
| 72 | 4.0 | 38.9 | 4.3 | 40.7 | 132 | 4.2 | 40.2 | 263 | 3.9 | 33.8 | 580 |
| 76 | 5.0 | 38.0 | 5.1 | 41.0 | 155 | 5.0 | 39.6 | 314 | 4.3 | 34.4 | 630 |
| 80 | 4.6 | 39.2 | 4.4 | 42.0 | 131 | 4.5 | 41.3 | 271 | 3.9 | 35.1 | 561 |
| 84 | 4.8 | 41.4 | 4.6 | 44.1 | 131 | 4.8 | 42.4 | 282 | 4.1 | 34.9 | 587 |
| 88 | 4.6 | 39.3 | 4.9 | 41.5 | 147 | 5.1 | 40.0 | 317 | 4.5 | 34.6 | 651 |
| 92 | 4.9 | 39.3 | 5.3 | 40.7 | 164 | 4.9 | 41.5 | 296 | 4.2 | 34.7 | 612 |
| 96 | 4.2 | 39.2 | 4.3 | 40.4 | 134 | 4.4 | 39.1 | 284 | 4.1 | 33.7 | 607 |
| 100 | 4.7 | 38.9 | 4.7 | 39.3 | 150 | 5.0 | 40.2 | 312 | 4.1 | 34.7 | 587 |
| 104 | 4.5 | 38.5 | 4.6 | 39.1 | 148 | 4.2 | 38.9 | 270 | 3.7 | 32.9 | 557 |
| **Mean for weeks** | | | | | | | | | | | |
| 4-13 | 3.8 | 21.7 | 4.0 | 22.7 | 223 | 4.0 | 22.5 | 452 | 3.8 | 20.9 | 907 |
| 14-52 | 4.2 | 34.6 | 4.2 | 35.6 | 150 | 4.2 | 34.9 | 300 | 3.9 | 29.9 | 659 |
| 53-104 | 4.5 | 39.0 | 4.6 | 40.8 | 143 | 4.6 | 40.1 | 287 | 4.1 | 34.3 | 598 |

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p*-nitrotoluene consumed per kilogram body weight per day

# APPENDIX I
# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

**TABLE I1**
**Ingredients of NTP-2000 Rat and Mouse Ration**

| Ingredients | Percent by Weight |
|---|---|
| Ground hard winter wheat | 22.26 |
| Ground #2 yellow shelled corn | 22.18 |
| Wheat middlings | 15.0 |
| Oat hulls | 8.5 |
| Alfalfa meal (dehydrated, 17% protein) | 7.5 |
| Purified cellulose | 5.5 |
| Soybean meal (49% protein) | 5.0 |
| Fish meal (60% protein) | 4.0 |
| Corn oil (without preservatives) | 3.0 |
| Soy oil (without preservatives) | 3.0 |
| Dried brewer's yeast | 1.0 |
| Calcium carbonate (USP) | 0.9 |
| Vitamin premix[a] | 0.5 |
| Mineral premix[b] | 0.5 |
| Calcium phosphate, dibasic (USP) | 0.4 |
| Sodium chloride | 0.3 |
| Choline chloride (70% choline) | 0.26 |
| Methionine | 0.2 |

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

**TABLE I2**
**Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]**

| | Amount | Source |
|---|---|---|
| **Vitamins** | | |
| A | 4,000 IU | Stabilized vitamin A palmitate or acetate |
| D | 1,000 IU | D-activated animal sterol |
| K | 1.0 mg | Menadione sodium bisulfite complex |
| α-Tocopheryl acetate | 100 IU | |
| Niacin | 23 mg | |
| Folic acid | 1.1 mg | |
| *d*-Pantothenic acid | 10 mg | *d*-Calcium pantothenate |
| Riboflavin | 3.3 mg | |
| Thiamine | 4 mg | Thiamine mononitrate |
| $B_{12}$ | 52 µg | |
| Pyridoxine | 6.3 mg | Pyridoxine hydrochloride |
| Biotin | 0.2 mg | *d*-Biotin |
| **Minerals** | | |
| Magnesium | 514 mg | Magnesium oxide |
| Iron | 35 mg | Iron sulfate |
| Zinc | 12 mg | Zinc oxide |
| Manganese | 10 mg | Manganese oxide |
| Copper | 2.0 mg | Copper sulfate |
| Iodine | 0.2 mg | Calcium iodate |
| Chromium | 0.2 mg | Chromium acetate |

[a] Per kg of finished product

**TABLE I3**
**Nutrient Composition of NTP-2000 Rat and Mouse Ration**

| Nutrient | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Protein (% by weight) | 13.6 ± 0.55 | 12.6 – 14.7 | 24 |
| Crude fat (% by weight) | 8.1 ± 0.32 | 7.5 – 9.0 | 24 |
| Crude fiber (% by weight) | 9.7 ± 0.64 | 8.4 – 11.1 | 24 |
| Ash (% by weight) | 5.1 ± 0.29 | 4.6 – 5.9 | 24 |
| **Amino Acids (% of total diet)** | | | |
| Arginine | 0.731 ± 0.050 | 0.670 – 0.800 | 8 |
| Cystine | 0.224 ± 0.012 | 0.210 – 0.240 | 8 |
| Glycine | 0.684 ± 0.041 | 0.620 – 0.740 | 8 |
| Histidine | 0.333 ± 0.018 | 0.310 – 0.350 | 8 |
| Isoleucine | 0.524 ± 0.046 | 0.430 – 0.590 | 8 |
| Leucine | 1.061 ± 0.061 | 0.960 – 1.130 | 8 |
| Lysine | 0.708 ± 0.056 | 0.620 – 0.790 | 8 |
| Methionine | 0.401 ± 0.035 | 0.350 – 0.460 | 8 |
| Phenylalanine | 0.598 ± 0.036 | 0.540 – 0.640 | 8 |
| Threonine | 0.501 ± 0.051 | 0.430 – 0.590 | 8 |
| Tryptophan | 0.126 ± 0.014 | 0.110 – 0.150 | 8 |
| Tyrosine | 0.390 ± 0.056 | 0.280 – 0.460 | 8 |
| Valine | 0.640 ± 0.049 | 0.550 – 0.690 | 8 |
| **Essential Fatty Acids (% of total diet)** | | | |
| Linoleic | 3.97 ± 0.284 | 3.59 – 4.54 | 8 |
| Linolenic | 0.30 ± 0.042 | 0.21 – 0.35 | 8 |
| **Vitamins** | | | |
| Vitamin A (IU/kg) | 4,699 ± 1,320 | 2,570 – 8,140 | 24 |
| Vitamin D (IU/kg) | 1,000[a] | | |
| $\alpha$-Tocopherol (ppm) | 82.2 ± 14.08 | 62.2 – 107.0 | 6 |
| Thiamine (ppm)[b] | 8.7 ± 1.24 | 6.6 – 11.7 | 24 |
| Riboflavin (ppm) | 5.6 ± 1.12 | 4.20 – 7.70 | 6 |
| Niacin (ppm) | 74.3 ± 5.94 | 66.4 – 85.8 | 6 |
| Pantothenic acid (ppm) | 22.5 ± 3.96 | 17.4 – 29.1 | 6 |
| Pyridoxine (ppm)[b] | 9.04 ± 2.37 | 6.4 – 12.4 | 6 |
| Folic acid (ppm) | 1.64 ± 0.38 | 1.26 – 2.32 | 6 |
| Biotin (ppm) | 0.333 ± 0.15 | 0.225 – 0.704 | 6 |
| Vitamin $B_{12}$ (ppb) | 68.7 ± 63.0 | 18.3 – 174.0 | 6 |
| Choline (as chloride) (ppm) | 3,155 ± 325 | 2,700 – 3,400 | 6 |
| **Minerals** | | | |
| Calcium (%) | 0.989 ± 0.050 | 0.884 – 1.080 | 24 |
| Phosphorus (%) | 0.581 ± 0.025 | 0.548 – 0.640 | 24 |
| Potassium (%) | 0.660 ± 0.026 | 0.627 – 0.691 | 6 |
| Chloride (%) | 0.356 ± 0.031 | 0.300 – 0.392 | 6 |
| Sodium (%) | 0.193 ± 0.020 | 0.160 – 0.212 | 6 |
| Magnesium (%) | 0.197 ± 0.010 | 0.185 – 0.213 | 6 |
| Sulfur (%) | 0.182 ± 0.023 | 0.153 – 0.209 | 6 |
| Iron (ppm) | 158 ± 15.2 | 135 – 173 | 6 |
| Manganese (ppm) | 51.8 ± 4.05 | 46.2 – 56.0 | 6 |
| Zinc (ppm) | 53.2 ± 5.68 | 45.0 – 61.1 | 6 |
| Copper (ppm) | 6.49 ± 0.786 | 5.38 – 7.59 | 6 |
| Iodine (ppm) | 0.487 ± 0.204 | 0.233 – 0.843 | 6 |
| Chromium (ppm) | 0.763 ± 0.620 | 0.330 – 2.000 | 6 |
| Cobalt (ppm) | 0.53 ± 0.720 | 0.20 – 2.0 | 6 |

[a] From formulation
[b] As hydrochloride

**TABLE I4**
**Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]**

| | Mean ± Standard Deviation[b] | Range | Number of Samples |
|---|---|---|---|
| **Contaminants** | | | |
| Arsenic (ppm) | 0.25 ± 0.097 | 0.10 – 0.50 | 24 |
| Cadmium (ppm) | 0.05 ± 0.011 | 0.04 – 0.90 | 24 |
| Lead (ppm) | 0.13 ± 0.097 | 0.06 – 0.40 | 24 |
| Mercury (ppm) | <0.02 | | 24 |
| Selenium (ppm) | 0.17 ± 0.033 | 0.12 – 0.24 | 24 |
| Aflatoxins (ppb) | <5.00 | | 24 |
| Nitrate nitrogen (ppm)[c] | 13.6 ± 5.37 | 6.5 – 33.6 | 24 |
| Nitrite nitrogen (ppm)[c] | 0.81 ± 0.650 | 0.30 – 3.20 | 24 |
| BHA (ppm)[d] | 1.2 ± 0.74 | 0.01 – 3.50 | 24 |
| BHT (ppm)[d] | 1.1 ± 0.48 | 0.01 – 2.30 | 24 |
| Aerobic plate count (CFU/g)[e] | 241,571 ± 194,051 | 46,000 – 590,000 | 7 |
| Coliform (MPN/g)[e] | 119 ± 176 | 9 – 510 | 7 |
| *Escherichia coli* (MPN/g) | <10 | | 24 |
| *Salmonella* (MPN/g) | Negative | | 24 |
| Total nitrosoamines (ppb)[f] | 5.4 ± 2.44 | 2.7 – 12.6 | 24 |
| *N*-Nitrosodimethylamine (ppb)[f] | 2.6 ± 1.78 | 0.9 – 6.6 | 24 |
| *N*-Nitrosopyrrolidine (ppb)[f] | 2.8 ± 1.62 | 1.1 – 8.7 | 24 |
| **Pesticides (ppm)** | | | |
| α-BHC | <0.01 | | 24 |
| β-BHC | <0.02 | | 24 |
| γ-BHC | <0.01 | | 24 |
| δ-BHC | <0.01 | | 24 |
| Heptachlor | <0.01 | | 24 |
| Aldrin | <0.01 | | 24 |
| Heptachlor epoxide | <0.01 | | 24 |
| DDE | <0.01 | | 24 |
| DDD | <0.01 | | 24 |
| DDT | <0.01 | | 24 |
| HCB | <0.01 | | 24 |
| Mirex | <0.01 | | 24 |
| Methoxychlor | <0.05 | | 24 |
| Dieldrin | <0.01 | | 24 |
| Endrin | <0.01 | | 24 |
| Telodrin | <0.01 | | 24 |
| Chlordane | <0.05 | | 24 |
| Toxaphene | <0.10 | | 24 |
| Estimated PCBs | <0.20 | | 24 |
| Ronnel | <0.01 | | 24 |
| Ethion | <0.02 | | 24 |
| Trithion | <0.05 | | 24 |
| Diazinon | <0.10 | | 24 |
| Methyl chlorpyrifos | 0.085 ± 0.088 | 0.010 – 0.300 | 20 |
| Methyl parathion | <0.02 | | 24 |
| Ethyl parathion | <0.02 | | 24 |
| Malathion | 0.140 ± 0.145 | 0.020 – 0.600 | 24 |
| Endosulfan I | <0.01 | | 24 |
| Endosulfan IQ | <0.01 | | 24 |
| Endosulfan sulfate | <0.03 | | 24 |

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] Nonirradiated samples. Microbial counts for irradiated samples were below the detection limit.
[f] All values were corrected for percent recovery.

# APPENDIX J
# SENTINEL ANIMAL PROGRAM

# SENTINEL ANIMAL PROGRAM

## METHODS

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

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Rockville, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed. At 18 months, live mice were shipped to MA Bioservices (Rockville, MD) for evaluation of bacterial profile and viral serology according to NIEHS Advisory Number 19.

| Method and Test | Time of Analysis |
|---|---|
| **RATS** | |
| **2-Year Study** | |
| ELISA | |
| *Mycoplasma pulmonis* | Study termination |
| PVM (pneumonia virus of mice) | 6, 12, and 18 months, study termination |
| RCV/SDA | |
| (rat coronavirus/sialodacryoadenitis virus) | 6, 12, and 18 months, study termination |
| Sendai | 6, 12, and 18 months, study termination |
| Immunofluorescence Assay | |
| *Helicobacter hepaticus* | 12 months |
| *Mycoplasma arthriditis* | Study termination |
| Parvovirus | Study termination |
| Hemagglutination Inhibition | |
| H-1 (Toolan's H-1 virus) | 6, 12, and 18 months |
| KRV (Kilham rat virus) | 6, 12, and 18 months |

## MICE

**2-Year Study**

| | |
|---|---|
| Bacterial Assays | |
| Oral | 18 months |
| Fecal | 18 months |
| *Helicobacter spp.* | 18 months |
| ELISA | |
| Ectromelia virus | 6, 12, and 18 months, study termination |
| EDIM (epizootic diarrhea of infant mice) | 6, 12, and 18 months, study termination |
| GDVII (mouse encephalomyelitis virus) | 6, 12, and 18 months, study termination |
| LCM (lymphocytic choriomeningitis virus) | 6, 12, and 18 months, study termination |
| Mouse adenoma virus-FL | 6, 12, and 18 months, study termination |
| *M. arthritidis* | 18 months and study termination |
| *M. pulmonis* | 18 months and study termination |
| MHV (mouse hepatitis virus) | 6, 12, and 18 months, study termination |
| PVM | 6, 12, and 18 months, study termination |
| Reovirus 3 | 6, 12, and 18 months, study termination |
| Sendai | 6, 12, and 18 months, study termination |
| Immunofluorescence Assay | |
| GDVII | Study termination |
| *H. hepaticus* | 18 months |
| LCM | 12 and 18 months |
| *M. arthriditis* | Study termination |
| Mouse adenoma virus-FL | 18 months |
| MCMV (mouse cytomegalovirus) | 18 months and study termination |
| Parvovirus | Study termination |
| Hemagglutination Inhibition | |
| K (papovavirus) | 6, 12, and 18 months |
| MVM (minute virus of mice) | 6, 12, and 18 months |
| Polyoma virus | 6, 12, and 18 months |

## RESULTS

For the 2-year study in rats, all serology tests were negative. At 18 months, no primary bacterial pathogens were detected by aerobic culture techniques in five male and five female mice that had been shipped live to the laboratory. These mice were subjected to comprehensive health evaluations including histologic evaluation of liver sections by special stains for *Helicobacter* infections. There was no evidence of infection by viral or parasitic organisms in these animals, and *Helicobacter spp.* were not isolated from any of these mice. One male mouse had a positive titer for *M. arthritidis* at study termination. Further evaluation of the sample positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only one sample was positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in the animal with the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered a false positive.

# APPENDIX K
# COMPARATIVE METABOLISM STUDIES OF *p*-NITROTOLUENE

# COMPARATIVE METABOLISM STUDIES OF *p*-NITROTOLUENE

## INTRODUCTION

*p*-Nitrotoluene is a colorless crystalline solid used in the manufacture of dyes and as a chemical intermediate in the synthesis of agricultural chemicals and rubber (*Kirk-Othmer*, 1981). Studies were conducted in F344/N rats and B6C3F$_1$ mice to determine and compare the metabolism and excretion of *p*-nitrotoluene following the administration of single and repeated doses in corn oil by gavage. These studies were conducted by Research Triangle Institute (Research Triangle Park, NC).

## MATERIALS AND METHODS

Nonradiolabeled *p*-nitrotoluene (99% pure) was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (KGO8727KF). Radiolabeled *p*-nitrotoluene (lot 3104-192, 17.8 mCi/mmol, 5.7 mCi), uniformly labeled with carbon-14 in the phenyl ring and with a stated radiochemical purity of 99%, was obtained from DuPont NEN Research Products (Boston, MA). For use as standards for metabolite identification, *p*-aminohippuric acid, *p*-nitrobenzoic acid, *p*-nitrobenzaldehyde, *p*-toluidine, 5-methyl-2-nitrophenol, and 2-methyl-5-nitrophenol were obtained from Aldrich Chemical Company. *p*-Aminobenzoic acid, *p*-acetamidobenzoic acid, *p*-nitrobenzyl alcohol, and S-(*p*-nitrobenzyl)glutathione were obtained from Sigma Chemical Company (St. Louis, MO). *p*-Nitrobenzylmercapturic acid was synthesized from *N*-acetyl-L-cysteine and *p*-nitrobenzyl bromide.

Radiochemical purity of the [$^{14}$C]-*p*-nitrotoluene was determined to be 96% or greater by the study laboratory using high-performance liquid chromatography (HPLC), a radioactivity detector with a scintillator flow cell, and ultraviolet detection at 275 nm. Homogeneity and stability analyses were performed on a 200 mg/kg [$^{14}$C]-*p*-nitrotoluene formulation in corn oil after 0, 6, and 24 hours and 13 days. Homogeneity was confirmed by liquid scintillation spectrometry. Stability was confirmed for 13 days using HPLC.

Male (62 to 73 days old at receipt) and female (71 to 104 days old at receipt) F344/N rats and B6C3F$_1$ mice (64 to 82 days old at receipt) were obtained from Charles River Laboratories (Raleigh, NC, and Kingston, NY). The animals were quarantined for at least 1 week before the beginning of each study. Prior to the metabolism studies, rats and mice were individually housed in polycarbonate cages containing Ab-Sorb-Dri® hardwood bedding chips (Lab Products, Maywood, NJ). During the 200 mg/kg pharmacokinetic studies, rats and mice were housed in polycarbonate cages before and after dosing. Animals in other metabolism studies were individually housed in glass metabolism cages which provided for separate collection of urine and feces. Animals received certified Purina Rodent Chow (#5002) and tap water *ad libitum*. In all studies, the dosing volume was 5 mL/kg body weight. Each rat received 10 to 20 µCi $^{14}$C and each mouse received 2 to 4 µCi $^{14}$C.

Urine and feces collected from the metabolism cages were stored on dry ice; the urine collection flasks were rinsed with distilled, deionized water which was added to the urine samples. At the end of the urine collection period for rats and at 24-hour intervals for mice in the single-dose studies, cages were rinsed with water and ethanol, and the rinses were also collected. Urine samples were also collected directly from the bladder of rats at termination.

Rats, except those in the biliary excretion study, were anesthetized with an intramuscular injection of ketamine:xylazine:acepromazine (10:1:1) or ketoxime:xylazine (1:1) prior to insertion of the jugular cannula and prior to final blood collection. Rats in the biliary excretion study were anesthetized with an intraperitoneal injection and oral dose of sodium pentobarbital prior to insertion of the bile duct cannula. Anesthetized rats fitted with an indwelling jugular cannula were euthanized by introduction of sodium pentobarbital into the cannula. All

other anesthetized rats were euthanized by intracardiac injection of sodium pentobarbital. Mice were anesthetized with an intramuscular injection of sodium pentobarbital and euthanized by cervical dislocation.

### Determination of Excretion and Urinary Metabolites of [$^{14}$C]-*p*-Nitrotoluene in Rats and Mice

Groups of three or four male and three or four female rats and mice were administered single gavage doses of 2 or 200 mg [$^{14}$C]-*p*-nitrotoluene/kg body weight in corn oil. Radioactivity was measured in urine collected 4 (rats only), 8, 24, 48, and 72 hours after dosing and feces collected 24, 48, and 72 hours after dosing. Total radiolabel in urine and feces was quantified by liquid scintillation spectrometry. Urinary metabolites were quantitated and identified by HPLC using a C-18 column. A mobile phase of A) acetonitrile:0.1% trifluoroacetic acid and B) water:0.1% trifluoroacetic acid was used with two flow rate programs. In the first flow rate program (method A), the mobile phase was 100% B for 4 minutes, changed linearly to 15% A:85% B over 3 minutes, changed linearly to 20% A:80% B over 3 minutes, held for 15 minutes, and then changed linearly to 50% A:50% B over 8 minutes. In the second flow rate program (method B), the mobile phase was held at 10% A:90% B for 2 minutes, changed linearly to 25% A:75% B over 8 minutes, held 8 minutes, changed linearly to 90% A:10% B over 2 minutes, and held for 2 minutes. For both flow rate programs, detection of metabolites was by UV absorption (254 nm). For quantitation, fractions of the column effluent were collected and counted in a liquid scintillation counter. Peak identity was established by coinjection of part of the collected fraction with a standard.

### Determination of Total Radiolabel in Blood and Plasma and Plasma Concentration of *p*-Nitrotoluene in Rats and Mice

Groups of three or four male and three or four female rats received a single gavage dose of 2 or 200 mg/kg [$^{14}$C]-*p*-nitrotoluene in corn oil. For the 2 mg/kg study and the first 200 mg/kg study in rats, blood and plasma samples were analyzed for radiolabel concentrations. For these studies, serial blood samples were obtained from rats via an indwelling jugular cannula at 2, 4, 6, 8, and 24 hours and by cardiac puncture at terminal sacrifice at 72 hours and analyzed for radiolabel concentration. A volume of heparinized saline equal to the volume of blood withdrawn was introduced into the cannula after each serial bleeding. In a second 200 mg/kg study in rats, plasma concentrations of *p*-nitrotoluene were measured using gas chromatography at 5, 15, 30, 60, 120, 240, and 480 minutes after dosing.

Groups of three male and three female mice received a single gavage dose of 200 mg/kg [$^{14}$C]-*p*-nitrotoluene in corn oil. Blood was collected from separate animals 5, 10, 20, 40, 60, 90, 120, 240, 480, and 1,440 minutes after dosing; blood and plasma were analyzed for concentrations of radiolabel by liquid scintillation spectrometry. Plasma concentrations of *p*-nitrotoluene were also determined in samples taken 5, 10, 20, 40, 60, 90, 120, and 240 minutes after dosing using gas chromatography with *m*-nitrotoluene as an internal standard.

### Determination of Biliary Excretion of [$^{14}$C]-*p*-Nitrotoluene Metabolites

Six male rats received a single gavage dose of 200 mg/kg [$^{14}$C]-*p*-nitrotoluene in corn oil. Bile was collected via an indwelling cannula 30, 60, 90, 120, 180, 240, 300, and 360 minutes after dosing. Total radiolabel was measured by liquid scintillation spectrometry, and metabolites were identified by comparison with metabolite standards using HPLC.

### Determination of Effects of Repeated Administration on Metabolism and Excretion of [$^{14}$C]-*p*-Nitrotoluene

Five male rats received single daily gavage doses of 200 mg/kg *p*-nitrotoluene in corn oil for 12 days, with radiolabel added to the dose on days 1, 5, and 9. Liquid scintillation spectrometry was used to measure the cumulative excretion of radioactivity in urine 4, 8, 24, 48, 72, and 96 hours after each radiolabeled dose and in feces 24, 48, 72, and 96 hours after each radiolabeled dose. In addition, the urinary metabolic profile was measured by HPLC 24 hours after the day 5 dose and 4, 8, 24, and 48 hours after the day 9 dose.

# RESULTS AND DISCUSSION

## Excretion and Urinary Metabolites of [$^{14}$C]-*p*-Nitrotoluene in Rats and Mice

[$^{14}$C]-*p*-Nitrotoluene administered to rats by gavage was excreted primarily in urine (Table K1). More than 70% of the 2 and 200 mg/kg doses were recovered in urine in the first 24 hours after dosing. By 72 hours, more than 80% of the radioactivity was recovered in urine; only 2% to 5% was recovered in feces. There were no significant differences in the elimination of radioactivity between male and female rats or in proportional excretion between the 2 and 200 mg/kg doses. Chism *et al.* (1984) reported that in male Fischer 344 rats dosed orally with 200 mg/kg, approximately 83% of the dose was excreted after 72 hours, with 77% in the urine and 6% in the feces.

The rate of urinary excretion by mice was similar to that by rats, with more than 70% of the 2 and 200 mg/kg doses recovered in urine in the first 24 hours after dosing (Table K2). After 72 hours, males had excreted approximately 90% of each dose in urine and 7% in feces; females excreted approximately 80% in urine and 14% in feces. Mouse cage design resulted in a higher tendency for mouse fecal pellets to become wet with urine, which may account for the higher dose recovery in the feces of mice than rats.

The major metabolites excreted in the urine of male rats receiving 2 mg/kg were *p*-nitrobenzoic acid (30% of the dose), *p*-acetamidobenzoic acid (16%), *p*-nitrohippuric acid (14%), and *p*-nitrobenzylmercapturic acid (7%) (Table K3). Other metabolites more polar than *p*-acetamidobenzoic acid (labeled Region A) accounted for approximately 5% of the dose. Metabolites eluting between *p*-nitrohippuric acid and *p*-nitrobenzoic acid (labeled Region C) accounted for approximately 14% of the dose. The percentages of these metabolites excreted by females receiving 2 mg/kg was slightly different: *p*-nitrobenzoic acid, 47%; *p*-acetamidobenzoic acid, 9%; *p*-nitrohippuric acid, 8%; and *p*-nitrobenzylmercapturic acid, 1%. Metabolites in Region A accounted for 7% of the dose, and metabolites in Region C accounted for only 2%. The metabolite profile changed over time for both males and females. *p*-Nitrobenzoic acid was the prominent metabolite for the first 8 hours after dosing; in the period from 24 to 48 hours after dosing, very little *p*-nitrobenzoic acid was detected, while the metabolites in Region A became more pronounced.

Urinary metabolite profiles for rats receiving a single 200 mg/kg gavage dose were similar to those for animals receiving 2 mg/kg, except that females excreted a greater proportion of the dose as *p*-acetamidobenzoic acid, and a smaller proportion was excreted by males and females as Region A metabolites (Table K4). Females excreted less *p*-nitrobenzylmercapturic acid than males following either dose. The metabolites in Region A amounted to only 2% of the dose.

In a metabolism study of *p*-nitrotoluene in rats, Chism *et al.* (1984) reported that 28% of a 200 mg/kg oral dose excreted in the urine within 72 hours was *p*-nitrobenzoic acid, 27% was *p*-acetamidobenzoic acid, 13% was *p*-nitrohippuric acid, and approximately 4% was *p*-nitrobenzylmercapturic acid.

In mice receiving a single gavage dose of 2 mg/kg, the major urinary metabolite was 2-methyl-5-nitrophenyl glucuronide (approximately 38% of the dose; Table K5). Overall average concentrations for other metabolites in mice included 2-methyl-5-nitrophenyl sulfate (11%) and *p*-nitrohippuric acid (12%), as well as unassigned and poorly resolved polar metabolites (8%; labeled Region A), and smaller amounts of unidentified, less polar metabolites (2%; labeled Region B).

The overall averages of major metabolites excreted in mouse urine after a single 200 mg/kg gavage dose were *p*-nitrohippuric acid, 17%; 2-methyl-5-nitrophenyl sulfate, 16%; 2-methyl-5-nitrophenyl glucuronide, 16%; *p*-nitrobenzoic acid, 8%; and *p*-acetamidobenzoic acid, 6% (Table K6). Unassigned and poorly resolved polar metabolites (Region A) accounted for approximately 8% of the dose, and unidentified, less polar metabolites (Region B) were less than 1% of the dose.

The conjugates 2-methyl-5-nitrophenyl glucuronide and 2-methyl-5-nitrophenyl sulfate have not been reported previously as *p*-nitrotoluene metabolites in any species, although Chism *et al.* (1984) reported that glucuronide and sulfate conjugates of the isomer 5-methyl-2-nitrophenol were very minor urinary metabolites in male rats following a 200 mg/kg oral dose.

In summary, the rates of [$^{14}$C]-*p*-nitrotoluene excretion following oral administration to rats and mice appeared quite similar, with more than 70% of each dose excreted in the urine within 24 hours. The metabolic pathways, however, differed between rats and mice. Following both the 2 and 200 mg/kg doses, rats excreted 30% to 50% of the dose as *p*-nitrobenzoic acid, whereas mice excreted only 5% to 10% of the 200 mg/kg dose as *p*-nitrobenzoic acid. The percentage of each dose excreted as *p*-nitrohippuric acid was similar and ranged from 8% to 21% for rats and mice receiving either dose.

## Total Radiolabel in Blood and Plasma and Plasma Concentration of *p*-Nitrotoluene in Rats and Mice

Radioactivity was rapidly cleared from the blood and plasma of male and female rats receiving 2 mg/kg *p*-nitrotoluene (Table K7). The highest blood and plasma concentrations were observed 2 hours after dosing. In rats receiving 200 mg/kg, the highest concentrations of radiolabel in blood and plasma were reached approximately 6 hours after dosing. The concentrations remained high through 8 hours after dosing and then declined. At 72 hours after dosing, radioactivity had not cleared completely from blood or plasma of either males or females.

In the second 200 mg/kg gavage study in rats, average *p*-nitrotoluene concentrations in rat plasma rose to approximately 8,600 ng/g plasma 15 minutes after dosing (Table K8). The concentration decreased rapidly from that point; 8 hours after dosing, one male and no females had a concentration above the limit of quantitation (305 ng/g). The half-life of *p*-nitrotoluene in plasma was approximately 1 hour for females and slightly less for males.

In mice receiving a single 200 mg/kg gavage dose, the highest concentrations of radiolabel in blood and plasma were reached approximately 40 minutes after dosing in males and 20 minutes after dosing in females (Table K9). The concentrations then declined steadily.

The mean peak *p*-nitrotoluene concentrations in mouse plasma after a single 200 mg/kg gavage dose were 5,451 ng/g in males and 12,779 ng/g in females, both at 10 minutes after dosing (Table K10). The concentrations then rapidly declined. Variability in plasma concentrations at each time point was greater in mice than in rats, possibly due to differences in the amount of feed in the stomach of each mouse at the time of dosing and the fact that each plasma sample was obtained from a different mouse.

## Biliary Excretion of [$^{14}$C]-*p*-Nitrotoluene Metabolites

In bile-cannulated male rats, biliary excretion increased slowly for 2 hours and then reached a steady excretion rate of approximately 1.5% of the dose per hour (Table K11). Approximately 7% of the administered dose had been excreted in bile at the end of the 6-hour collection period. Because only 2% to 5% of the radiolabeled dose was recovered in the feces of rats in either the 2 or 200 mg/kg single-dose studies, some reabsorption of radiolabel may have occurred in the lower gastrointestinal tract. Of the approximately 7% of the dose excreted in the first 6 hours after dosing, the major metabolites were *p*-nitrobenzoic acid (2.5%), S-(*p*-nitrobenzyl)-glutathione (4.4%), and *p*-nitrobenzyl glucuronide (0.4%) (Table K12). Glutathione concentrations may have been depleted following the dose; as S-(*p*-nitrobenzyl)-glutathione concentrations in the bile decreased, *p*-nitrobenzoic acid concentrations increased. Chism and Rickert (1985) reported that 9.8% of a 200 mg/kg oral dose of *p*-nitrotoluene was excreted in the bile within 12 hours as *p*-nitrobenzoic acid. S-(*p*-Nitrobenzyl)-glutathione accounted for 2.8% of the dose, and *p*-nitrobenzyl glucuronide accounted for 0.9% of the dose.

### Effects of Repeated Administration on Metabolism and Excretion of [$^{14}$C]-*p*-Nitrotoluene

No change in the rates and routes of excretion were observed during the 12-day study (Table K13). In addition, the urinary metabolite profile of rats in the repeated-dose study did not appear to change with successive doses (Table K14). After repeated dosing, the primary urinary metabolite, accounting for 40% to 50% of the radiolabel in urine at all collection times, was *p*-nitrobenzoic acid. *p*-Acetamidobenzoic acid, *p*-nitrohippuric acid, and *p*-nitrobenzylmercapturic acid were also present. At 24 hours or more after dosing, 4% to 7% of the radiolabel in urine eluted as a mix of more polar metabolites (labeled Regions A and B).

## REFERENCES

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Chism, J.P., Turner, M.J., Jr., and Rickert, D.E. (1984). The metabolism and excretion of mononitrotoluenes by Fischer 344 rats. *Drug Metab. Dispos.* **12**, 596-602.

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**TABLE K1**
**Cumulative Excretion of Radioactivity by F344/N Rats after a Single Gavage Dose of [$^{14}$C]-*p*-Nitrotoluene**[a]

| | Time (hours after dosing) | Urine | Feces | Total |
|---|---|---|---|---|
| **Male** | | | | |
| 2 mg/kg | | | | |
| | 4 | 21.5 ± 26.1 | —[c] | 21.5 ± 26.1 |
| | 8 | 59.2 ± 5.5 | — | 59.2 ± 5.5 |
| | 24 | 90.3 ± 6.6 | 2.5 ± 1.1 | 92.9 ± 6.4 |
| | 48 | 93.7 ± 6.3 | 3.3 ± 1.0 | 97.0 ± 6.2 |
| | 72 | 95.3 ± 6.2[b] | 3.5 ± 1.0 | 98.8 ± 6.0 |
| 200 mg/kg | | | | |
| | 4 | 7.4 ± 8.5 | — | 7.4 ± 8.5 |
| | 8 | 34.0 ± 11.3 | — | 34.0 ± 11.3 |
| | 24 | 81.1 ± 5.1 | 2.9 ± 3.2 | 84.0 ± 3.7 |
| | 48 | 84.9 ± 4.2 | 3.6 ± 3.2 | 88.5 ± 1.5 |
| | 72 | 87.2 ± 3.9 | 4.7 ± 2.9 | 92.0 ± 1.1 |
| **Female** | | | | |
| 2 mg/kg | | | | |
| | 4 | 0.0 ± 0.0 | — | 0.0 ± 0.0 |
| | 8 | 17.1 ± 23.4 | — | 17.1 ± 23.4 |
| | 24 | 73.8 ± 10.7 | 3.3 ± 3.4 | 77.1 ± 11.4 |
| | 48 | 80.1 ± 9.7 | 4.7 ± 3.7 | 84.8 ± 11.4 |
| | 72 | 82.6 ± 9.7[b] | 5.0 ± 3.6 | 87.6 ± 11.1 |
| 200 mg/kg | | | | |
| | 4 | 7.8 ± 6.2 | — | 7.8 ± 6.2 |
| | 8 | 27.1 ± 10.1 | — | 27.1 ± 10.1 |
| | 24 | 79.7 ± 11.2 | 1.1 ± 1.4 | 80.7 ± 9.7 |
| | 48 | 83.7 ± 10.0 | 2.2 ± 1.4 | 85.9 ± 8.7 |
| | 72 | 85.2 ± 9.9 | 2.5 ± 1.5 | 87.7 ± 8.4 |

[a] Four animals were sampled at each time point; data are presented as cumulative percentage of dose (mean ± standard deviation). Urine values at the 72-hour time points include cage rinse.
[b] Value includes urine taken directly from the bladder.
[c] No data available; feces were collected at 24-hour intervals.

**TABLE K2**
**Cumulative Excretion of Radioactivity by B6C3F$_1$ Mice after a Single Gavage Dose of [$^{14}$C]-*p*-Nitrotoluene**[a]

| | Time (hours after dosing) | Urine | Feces | Total |
|---|---|---|---|---|
| **Male** | | | | |
| 2 mg/kg | | | | |
| | 8 | 0.0 ± 0.0 | —[b] | 0.0 ± 0.0 |
| | 24 | 85.1 ± 2.4 | 5.7 ± 0.7 | 90.8 ± 1.7 |
| | 48 | 88.2 ± 3.1 | 6.7 ± 0.8 | 94.9 ± 2.4 |
| | 72 | 89.1 ± 2.4 | 6.8 ± 0.9 | 95.9 ± 1.6 |
| 200 mg/kg | | | | |
| | 8 | 15.3 ± 26.4 | — | 15.3 ± 26.4 |
| | 24 | 87.9 ± 3.4 | 5.1 ± 0.5 | 93.0 ± 3.1 |
| | 48 | 90.7 ± 1.7 | 5.9 ± 0.5 | 96.7 ± 1.3 |
| | 72 | 91.1 ± 1.8 | 6.1 ± 0.5 | 97.2 ± 1.2 |
| **Female** | | | | |
| 2 mg/kg | | | | |
| | 8 | 25.2 ± 24.4 | — | 25.2 ± 24.4 |
| | 24 | 70.5 ± 15.8 | 14.2 ± 11.0 | 84.7 ± 9.5 |
| | 48 | 76.1 ± 14.6 | 16.2 ± 11.4 | 92.3 ± 4.6 |
| | 72 | 76.9 ± 14.6 | 16.8 ± 11.7 | 93.7 ± 3.8 |
| 200 mg/kg | | | | |
| | 8 | 8.2 ± 11.4 | — | 8.2 ± 11.4 |
| | 24 | 76.9 ± 5.7 | 9.0 ± 6.1 | 85.9 ± 0.8 |
| | 48 | 82.2 ± 5.6 | 10.7 ± 6.3 | 92.9 ± 1.0 |
| | 72 | 83.3 ± 5.7 | 11.2 ± 6.5 | 94.5 ± 1.0 |

[a] Three animals were sampled at each time point; data are presented as cumulative percentage of dose (mean ± standard deviation).
[b] Urine values at the 24-, 48-, and 72-hour time points include cage rinse.
No data available; feces were collected at 24-hour intervals.

**TABLE K3**
**Urinary Metabolite Profile for F344/N Rats after a Single Gavage Dose of 2 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (hours after dosing) | Percentage of Dose Excreted in Urine | Region A[b] | *p*-Acetamidobenzoic Acid | *p*-Nitrohippuric Acid | Region C[c] | *p*-Nitrobenzoic Acid | *p*-Nitrobenzyl Mercapturate |
|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | |
| 8 | 58.1 ± 6.2 | 0.0 ± 0.0 | 8.9 ± 3.5 | 10.4 ± 2.4 | 4.4 ± 0.1 | 26.3 ± 4.2 | 4.6 ± 0.9 |
| 24 | 29.1 ± 7.9 | 3.0 ± 1.3 | 7.0 ± 0.7 | 3.3 ± 0.8 | 9.6 ± 4.5 | 3.3 ± 0.8 | 2.4 ± 0.8 |
| 48 | 3.4 ± 1.4 | 2.2 ± 1.0 | 0.3 ± 0.1 | 0.2 ± 0.3 | 0.1 ± 0.1 | 0.2 ± 0.1 | 0.3 ± 0.1 |
| Total[d] | 92.3 ± 1.3 | 5.2 ± 0.5 | 16.1 ± 3.8 | 13.9 ± 2.0 | 14.1 ± 4.5 | 29.8 ± 5.0 | 7.2 ± 0.2 |
| **Female** | | | | | | | |
| 8[e] | 22.9 ± 25.0 | 0.0 | 3.7 | 4.1 | 1.1 | 23.7 | 0.6 |
| 24 | 46.0 ± 28.5 | 1.7 ± 1.0 | 6.2 ± 2.8 | 5.0 ± 4.1 | 0.7 ± 0.8 | 30.6 ± 18.8 | 0.6 ± 0.4 |
| 48 | 7.6 ± 5.3 | 5.8 ± 4.1 | 0.1 ± 0.2 | 0.5 ± 0.6 | 0.3 ± 0.2 | 0.5 ± 0.4 | 0.2 ± 0.1 |
| Total | 78.9 ± 9.1 | 7.4 ± 5.0 | 8.8 ± 0.2 | 8.2 ± 2.5 | 1.6 ± 0.7 | 47.0 ± 2.2 | 1.2 ± 0.2 |

[a] Three animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Retention time approximately 2 to 4 minutes using method A
[c] Retention time approximately 14.5 minutes using method A
[d] Mean of individual animal cumulative urinary excretion from 0 to 48 hours
[e] n=2 for metabolite data; standard deviation not calculated because of an insufficient number of samples

**TABLE K4**
**Urinary Metabolite Profile for F344/N Rats after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (hours after dosing) | Percentage of Dose Excreted in Urine | Region A[b] | Region B[c] | *p*-Acetamido-benzoic Acid | *p*-Nitrohippuric Acid | Region C[d] | *p*-Nitrobenzoic Acid | *p*-Nitrobenzyl Mercapturate |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| 8 | 36.3 ± 12.7 | 0.0 ± 0.0 | 0.0 ± 0.0 | 4.9 ± 2.0 | 4.9 ± 1.5 | 1.1 ± 0.4 | 20.7 ± 8.4 | 4.1 ± 1.5 |
| 24 | 46.6 ± 11.4 | 0.0 ± 0.0 | 1.3 ± 0.7 | 10.5 ± 1.0 | 5.1 ± 2.0 | 10.7 ± 10.0 | 15.2 ± 3.3 | 2.9 ± 1.0 |
| 48 | 4.0 ± 2.8 | 2.4 ± 2.5 | 0.0 ± 0.0 | 0.6 ± 0.5 | 0.4 ± 0.2 | 0.1 ± 0.1 | 0.3 ± 0.2 | 0.1 ± 0.1 |
| Total[e] | 89.1 ± 0.6 | 2.4 ± 2.5 | 1.3 ± 0.7 | 16.1 ± 2.6 | 10.3 ± 1.3 | 11.8 ± 9.6 | 36.2 ± 11.1 | 7.1 ± 0.4 |
| **Female** | | | | | | | | |
| 8 | 24.0 ± 9.9 | 0.0 ± 0.0 | 0.0 ± 0.0 | 4.4 ± 2.0 | 3.1 ± 1.6 | 0.9 ± 0.4 | 14.9 ± 6.6 | 0.0 ± 0.0 |
| 24 | 53.7 ± 3.4 | 0.0 ± 0.0 | 2.6 ± 0.4 | 12.3 ± 5.3 | 5.1 ± 3.6 | 0.8 ± 0.1 | 29.7 ± 1.6 | 1.1 ± 0.2 |
| 48 | 4.4 ± 1.4 | 0.2 ± 0.1 | 0.0 ± 0.0 | 2.6 ± 1.6 | 0.5 ± 0.2 | 0.8 ± 0.5 | 0.3 ± 0.1 | 0.0 ± 0.1 |
| Total | 83.6 ± 11.4 | 0.2 ± 0.1 | 2.6 ± 0.3 | 19.3 ± 6.6 | 8.7 ± 3.5 | 2.6 ± 0.8 | 45.0 ± 8.2 | 1.2 ± 0.2 |

[a] Three animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Retention time approximately 2 to 4 minutes using method A
[c] Retention time approximately 11 minutes using method A
[d] Retention time approximately 14.5 minutes using method A
[e] Mean of individual animal cumulative urinary excretion from 0 to 48 hours

**TABLE K5**
**Urinary Metabolite Profile for B6C3F$_1$ Mice after a Single Gavage Dose of 2 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (hours after dosing) | Percentage of Dose Excreted in Urine | Region A[b] | *p*-Acetamido-benzoic Acid | *p*-Nitrohippuric Acid | 2-Methyl-5-nitrophenyl Glucuronide | 2-Methyl-5-nitrophenyl Sulfate | *p*-Nitrobenzoic Acid | Region B[c] |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| 8[d] | 0.0 ± 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 24 | 85.1 ± 2.4 | 12.0 ± 0.6 | 0.0 ± 0.0 | 9.8 ± 0.9 | 41.7 ± 2.9 | 11.1 ± 1.8 | 0.0 ± 0.0 | 2.1 ± 0.7 |
| 48[e] | 3.2 ± 1.0 | 0.9 | 0.1 | 0.0 | 0.5 | 0.1 | 0.0 | 0.1 |
| Total[f] | 88.2 ± 3.1 | 12.5 ± 0.4 | 0.0 ± 0.1 | 9.9 ± 0.9 | 42.0 ± 2.4 | 11.2 ± 1.9 | 0.0 ± 0.0 | 2.2 ± 0.8 |
| **Female** | | | | | | | | |
| 8 | 25.2 ± 24.4 | 0.8 ± 0.6 | 0.0 ± 0.0 | 5.4 ± 5.3 | 13.3 ± 13.2 | 4.3 ± 4.4 | 0.0 ± 0.0 | 0.3 ± 0.2 |
| 24 | 45.3 ± 8.6 | 3.0 ± 1.4 | 0.0 ± 0.0 | 8.7 ± 1.3 | 20.8 ± 3.4 | 7.2 ± 1.2 | 0.0 ± 0.0 | 1.6 ± 1.3 |
| 48[d] | 5.6 ± 4.2 | 0.6 | 0.1 | 0.5 | 1.1 | 0.1 | 0.0 | 0.4 |
| Total | 76.1 ± 14.7 | 4.0 ± 1.0 | 0.0 ± 0.1 | 14.2 ± 3.9 | 34.5 ± 10.0 | 11.5 ± 3.1 | 0.0 ± 0.0 | 1.9 ± 1.6 |

[a] Three animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Retention time approximately 2 to 6 minutes using method B
[c] Retention time approximately 19 to 23 minutes using method B
[d] n=1 for metabolite data
[e] n=2 for metabolite data; standard deviation not calculated because of an insufficient number of samples
[f] Mean of individual animal cumulative urinary excretion from 0 to 48 hours

**TABLE K6**
**Urinary Metabolite Profile for B6C3F$_1$ Mice after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (hours after dosing) | Percentage of Dose Excreted in Urine | Region A[b] | *p*-Acetamido-benzoic Acid | *p*-Nitrohippuric Acid | 2-Methyl-5-nitrophenyl Glucuronide | 2-Methyl-5-nitrophenyl Sulfate | *p*-Nitrobenzoic Acid | Region B[c] |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| 8[d] | 15.3 ± 26.4 | 3.7 | 3.3 | 9.7 | 4.0 | 10.1 | 3.4 | 0.4 |
| 24 | 72.6 ± 23.3 | 7.7 ± 1.9 | 2.9 ± 1.2 | 16.8 ± 6.7 | 11.1 ± 4.4 | 15.4 ± 6.1 | 4.3 ± 3.5 | 0.5 ± 0.6 |
| 48[d] | 2.9 ± 2.2 | 0.8 | 0.5 | 1.5 | 0.9 | 0.7 | 0.3 | 0.3 |
| Total[e] | 90.8 ± 1.7 | 9.2 ± 0.1 | 4.2 ± 2.3 | 20.5 ± 3.6 | 12.7 ± 2.3 | 19.0 ± 0.7 | 5.5 ± 3.5 | 0.8 ± 0.4 |
| **Female** | | | | | | | | |
| 8 | 8.2 ± 11.5 | 0.4 ± 0.6 | 0.5 ± 0.6 | 1.1 ± 1.5 | 0.6 ± 0.4 | 1.9 ± 2.7 | 1.4 ± 1.9 | 0.0 ± 0.1 |
| 24 | 68.8 ± 6.6 | 6.4 ± 2.3 | 6.4 ± 3.3 | 12.9 ± 2.0 | 15.5 ± 4.9 | 9.3 ± 1.4 | 8.9 ± 0.3 | 0.5 ± 0.2 |
| 48 | 5.3 ± 0.3 | 0.6 ± 0.1 | 0.2 ± 0.1 | 0.6 ± 0.0 | 2.6 ± 0.0 | 0.7 ± 0.2 | 0.1 ± 0.1 | 0.3 ± 0.1 |
| Total | 82.2 ± 5.6 | 7.4 ± 1.8 | 7.0 ± 2.7 | 14.7 ± 0.9 | 18.7 ± 5.1 | 12.0 ± 2.2 | 10.3 ± 2.0 | 0.8 ± 0.2 |

[a] Three animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Retention time approximately 2 to 6 minutes using method B
[c] Retention time approximately 19 to 23 minutes using method B
[d] n=1 for metabolite data
[e] Mean of individual animal cumulative urinary excretion from 0 to 48 hours

**TABLE K7**
**Blood and Plasma Concentrations of *p*-Nitrotoluene Equivalents in F344/N Rats after a Single Gavage Dose of [$^{14}$C]-*p*-Nitrotoluene**[a]

| | Time (hours after dosing) | Blood | Plasma |
|---|---|---|---|
| **Male** | | | |
| 2 mg/kg | | | |
| | 2 | 0.406 ± 0.113 | 0.745 ± 0.235 |
| | 4 | 0.250 ± 0.032 | 0.449 ± 0.073 |
| | 6 | 0.102 ± 0.047[b] | 0.146 ± 0.091 |
| | 8 | 0.054 ± 0.025 | 0.082 ± 0.049 |
| | 24 | 0.007 ± 0.001 | 0.010 ± 0.002 |
| | 72 | 0.004 ± 0.001 | 0.006 ± 0.001 |
| 200 mg/kg | | | |
| | 2 | 60.7 ± 8.96 | 89.1 ± 14.4 |
| | 4 | 87.0 ± 22.1 | 131 ± 28.2 |
| | 6 | 99.9 ± 16.8 | 145 ± 23 |
| | 8 | 97.4 ± 29.4 | 137 ± 37.4 |
| | 24 | 0.754 ± 0.130 | 0.71 ± 0.127 |
| | 72 | 0.277 ± 0.065 | 0.116 ± 0.079 |
| **Female** | | | |
| 2 mg/kg | | | |
| | 2 | 0.715 ± 0.238 | 1.28 ± 0.483 |
| | 4 | 0.173 ± 0.032 | 0.26 ± 0.061 |
| | 6 | 0.119 ± 0.023 | 0.177 ± 0.022 |
| | 8 | 0.081 ± 0.010 | 0.12 ± 0.017 |
| | 24 | 0.007 ± 0.001 | 0.009 ± 0.002 |
| | 72 | 0.003 ± 0.000 | 0.006 ± 0.002 |
| 200 mg/kg | | | |
| | 2 | 87.0 ± 11.3 | 120 ± 13.9 |
| | 4 | 102 ± 11.2 | 145 ± 12.8 |
| | 6 | 114 ± 28.0 | 160 ± 33.1 |
| | 8 | 115 ± 23.9 | 149 ± 22.2 |
| | 24 | 1.26 ± 0.46 | 1.55 ± 0.998 |
| | 72 | 0.254 ± 0.027 | 0.178 ± 0.117 |

[a] Four animals were sampled at each time point; data are presented as µg-Eq/g blood or plasma (mean ± standard deviation).
[b] n=3

**TABLE K8**
**Plasma Concentrations of *p*-Nitrotoluene in F344/N Rats after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (minutes after dosing) | Concentration (ng/g plasma) |
|---|---|
| **Male** | |
| 5 | 7,044 ± 1,787 |
| 15 | 8,637 ± 3,276 |
| 30 | 5,712 ± 2,055 |
| 60 | 2,877 ± 1,163 |
| 120 | 2,742 ± 1,645 |
| 240 | 612[b] |
| 480 | 313[c] |
| **Female** | |
| 5 | 8,657 ± 211 |
| 15 | 8,607 ± 622 |
| 30 | 5,106 ± 1,111 |
| 60 | 4,620 ± 2,339 |
| 120 | 2,057 ± 628 |
| 240 | 1,156 ± 635 |
| 480 | —[d] |

[a] Three animals were bled at each time point; data are presented as mean ± standard deviation.
[b] n=2; standard deviation not calculated because of an insufficient number of samples
[c] n=1
[d] Below limit of quantitation (305 ng/g)

**TABLE K9**
**Blood and Plasma Concentrations of *p*-Nitrotoluene Equivalents in B6C3F$_1$ Mice after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene**[a]

| Time (minutes after dosing) | Blood | Plasma |
|---|---|---|
| **Males** | | |
| 5 | 17.9 ± 14.5 | 26.8 ± 21.3 |
| 10 | 59.9 ± 11.2 | 91.0 ± 9.6 |
| 20 | 65.0 ± 48.8 | 104.0 ± 68.1 |
| 40 | 125.0 ± 53.1 | 183.0 ± 75.8 |
| 60 | 67.2 ± 23.2 | 97.0 ± 39.0 |
| 90 | 74.7 ± 5.0 | 93.8 ± 35.1 |
| 120 | 39.6 ± 16.0 | 83.7 ± 42.2 |
| 240 | 15.5 ± 6.5 | 25.1 ± 11.3 |
| 480 | 2.2 ± 0.5 | 2.8 ± 1.0 |
| 1,440 | 0.4 ± 0.0 | 0.2 ± 0.0 |
| **Females** | | |
| 5 | 8.2 ± 1.9 | 13.3 ± 2.3 |
| 10 | 82.8 ± 13.8 | 123.0 ± 19.2 |
| 20 | 131.0 ± 31.0 | 202.0 ± 46.2 |
| 40 | 88.1 ± 28.5 | 132.0 ± 42.3 |
| 60 | 121.0 ± 31.2 | 162.0 ± 52.1 |
| 90 | 80.9 ± 35.8 | 125.0 ± 50.6 |
| 120 | 62.8 ± 17.2 | 98.4 ± 29.2 |
| 240 | 50.3 ± 30.3 | 77.4 ± 43.2 |
| 480 | 8.0 ± 5.9 | 11.8 ± 8.4 |
| 1,440 | 0.5 ± 0.1 | 0.5 ± 0.2 |

[a] Three animals were bled at each time point; data are presented as µg-Eq/g blood or plasma (mean ± standard deviation).

**TABLE K10**
**Plasma Concentrations of *p*-Nitrotoluene in B6C3F$_1$ Mice after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (minutes after dosing) | Concentration (ng/g plasma) |
|---|---|
| **Male** | |
| 5 | 3,141 ± 2,593 |
| 10 | 5,451 ± 2,219 |
| 20 | 1,635[b] |
| 40 | 713[b] |
| 60 | 152[c] |
| 90 | 1,422[b] |
| 120 | 645[b] |
| 240 | 72.5[c] |
| **Female** | |
| 5 | 905 ± 383 |
| 10 | 12,779 ± 4,975 |
| 20 | 2,824 ± 3,036 |
| 40 | 480[b] |
| 60 | 1,313[b] |
| 90 | 400[b] |
| 120 | 382[c] |
| 240 | —[d] |

[a] Three animals were bled at each time point; data are presented as mean ± standard deviation.
[b] n=2; standard deviation not calculated because of an insufficient number of samples
[c] n=1
[d] Below limit of quantitation (145 ng/g)

**TABLE K11**
**Cumulative Excretion of Radioactivity in Bile of Male F344/N Rats after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (minutes after dosing) | Percentage Excreted |
|---|---|
| 30 | 0.4 ± 0.2 |
| 60 | 0.9 ± 0.4 |
| 90 | 1.5 ± 0.7 |
| 120 | 2.2 ± 1.0 |
| 180 | 3.6 ± 1.6 |
| 240 | 5.0 ± 1.6 |
| 300 | 6.2 ± 1.9 |
| 360 | 7.0 ± 1.7 |

[a] Five animals were sampled at each time point; data are presented as cumulative percentage of dose (mean ± standard deviation).

**TABLE K12**
**Biliary Metabolite Profile for Male F344/N Rats after a Single Gavage Dose of 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene[a]**

| Time (minutes after dosing) | Percentage of Dose Excreted in Bile | *p*-Nitrobenzyl Glucuronide | *p*-Nitrobenzoic Acid | S-(*p*-Nitrobenzyl)-Glutathione |
|---|---|---|---|---|
| 30 | 0.5 ± 0.1 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.4 ± 0.1 |
| 60 | 0.7 ± 0.2 | 0.0 ± 0.0 | 0.1 ± 0.0 | 0.6 ± 0.2 |
| 90 | 0.7 ± 0.1 | 0.0 ± 0.0 | 0.1 ± 0.1 | 0.6 ± 0.2 |
| 120 | 0.8 ± 0.2 | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.6 ± 0.2 |
| 180 | 1.7 ± 0.5 | 0.1 ± 0.1 | 0.5 ± 0.2 | 1.1 ± 0.6 |
| 240 | 1.4 ± 0.3 | 0.1 ± 0.1 | 0.6 ± 0.2 | 0.6 ± 0.3 |
| 300 | 1.3 ± 0.5 | 0.0 ± 0.1 | 0.7 ± 0.1 | 0.5 ± 0.4 |
| 360 | 0.7 ± 0.3 | 0.0 ± 0.0 | 0.5 ± 0.3 | 0.1 ± 0.1 |
| Total[b] | 7.7 ± 1.1 | 0.4 ± 0.0 | 2.5 ± 0.8 | 4.4 ± 1.4 |

[a] Three animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Mean of individual animal cumulative biliary excretion from 0 to 6 hours

**TABLE K13**
**Cumulative Excretion of Radioactivity by Male F344/N Rats Administered 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene in the 12-Day Gavage Study[a]**

| | Time (hours after dosing) | Urine | Feces | Total |
|---|---|---|---|---|
| **Day 1** | | | | |
| | 4 | 10.4 ± 5.7 | —[b] | 10.4 ± 5.7 |
| | 8 | 25.9 ± 9.0 | — | 25.9 ± 9.0 |
| | 24 | 84.0 ± 3.7 | 3.6 ± 1.0 | 87.6 ± 2.7 |
| | 48 | 90.0 ± 2.4 | 4.4 ± 1.0 | 94.4 ± 1.5 |
| | 72 | 90.1 ± 2.4 | 4.5 ± 1.0 | 94.5 ± 1.4 |
| | 96 | 90.1 ± 2.4 | 4.5 ± 1.0 | 94.6 ± 1.4 |
| **Day 5** | | | | |
| | 4 | 11.0 ± 9.5 | — | 11.0 ± 9.5 |
| | 8 | 34.3 ± 6.0 | — | 34.3 ± 6.0 |
| | 24 | 85.6 ± 3.2 | 3.1 ± 0.9 | 88.7 ± 2.4 |
| | 48 | 91.4 ± 1.7 | 3.6 ± 0.8 | 95.0 ± 1.3 |
| | 72 | 91.5 ± 1.7 | 3.6 ± 0.8 | 95.1 ± 1.3 |
| | 96 | 91.6 ± 1.7 | 3.6 ± 0.8 | 95.2 ± 1.3 |
| **Day 9** | | | | |
| | 4 | 11.9 ± 7.0 | — | 11.9 ± 7.0 |
| | 8 | 24.5 ± 8.6[d] | — | 24.5 ± 8.6 |
| | 24 | 82.6 ± 2.8 | 4.5 ± 2.1 | 87.2 ± 3.0 |
| | 48 | 87.9 ± 1.4 | 6.2 ± 2.3 | 94.1 ± 1.1 |
| | 72 | 88.0 ± 1.4 | 6.2 ± 2.4 | 94.3 ± 1.1[d] |
| | 96[c] | 88.1 ± 1.4[d] | 6.2 ± 2.4 | 94.3 ± 1.2 |

[a] Five animals were sampled at each time point; data are presented as cumulative percentage of dose (mean ± standard deviation).
[b] No data available; feces were collected at 24-hour intervals.
[c] n=3
[d] Value includes urine taken directly from the bladder.

**TABLE K14**
**Urinary Metabolite Profile for Male F344/N Rats Administered 200 mg/kg [$^{14}$C]-*p*-Nitrotoluene in the 12-Day Gavage Study[a]**

| | Time (hours after dosing) | Region A[b] | Region B[c] | *p*-Acetamidobenzoic Acid | *p*-Nitrohippuric Acid | *p*-Nitrobenzoic Acid | *p*-Nitrobenzyl Mercapturate |
|---|---|---|---|---|---|---|---|
| **Day 5** | | | | | | | |
| | 24 | 2.4 ± 0.5 | 3.3 ± 0.3 | 26.1 ± 1.6 | 11.7 ± 1.5 | 45.0 ± 2.2 | 3.8 ± 0.8 |
| **Day 9** | | | | | | | |
| | 4 | 0.9 ± 0.1 | 0.9 ± 0.1 | 8.5 ± 1.8 | 17.5 ± 1.6 | 51.1 ± 2.0 | 12.4 ± 1.1 |
| | 8 | 1.5 ± 0.5 | 1.8 ± 0.6 | 16.9 ± 5.2 | 16.4 ± 2.1 | 44.8 ± 8.0 | 10.1 ± 2.2 |
| | 24 | 2.3 ± 0.4 | 3.5 ± 0.7 | 23.9 ± 4.9 | 11.9 ± 2.2 | 44.5 ± 5.0 | 4.5 ± 1.1 |
| | 48[d] | 2.7 ± 0.4 | 3.8 ± 0.6 | 27.1 ± 1.1 | 12.0 ± 1.4 | 40.6 ± 0.6 | 4.8 ± 0.9 |

[a] Five animals were sampled at each time point; data are presented as percentage of dose excreted (mean ± standard deviation).
[b] Retention time approximately 2 to 4 minutes using method B
[c] Retention time approximately 4 to 6 minutes using method B
[d] n=3

# National Toxicology Program Technical Reports

## Printed as of May 2002

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